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FRANK BURR MALLORY

Frank Burr Mallory died on September 27, 1941 at the age of 78. He was a past president of the American Association of Pathologists and Bacteriologists and served as its treasurer from 1911 to 1940. In 1923 he became editor-in-chief of the JOURNAL OF MEDICAL RESEARCH. When that journal became the AMERICAN JOURNAL OF PATHOLOGY in 1925, he served in a similar capacity until 1940. It was under his direction that the AMERICAN JOURNAL OF PATHOLOGY attained the high position it holds among scientific periodicals.

Dr. Mallory graduated from Harvard College in 1886 and received the degrees of A.M. and M.D. from Harvard Medical School in 1890. He became associated with the Boston City Hospital in 1891 and continued this association up to the time of his death. He was made pathologist to this hospital in 1908 and served as such until his retirement in 1932 when he became consulting pathologist. The present pathological laboratory was named, in his honor, the "Mallory Institute of Pathology." He joined the teaching staff of the Harvard Medical School in 1890, was made assistant professor of pathology in 1896, and associate professor in 1901. In 1928 he was appointed professor of pathology, becoming emeritus professor in 1932.

Dr. Mallory was a member of numerous scientific societies in the United States and also was a corresponding member of the Royal Medical Society of Budapest. He received the honorary degree of Sc.D. from Tufts College in 1928 and a similar degree from Boston University in 1932. In 1935 he was awarded the Kober medal by the Association of American Physicians for outstanding service in pathology. He was the third individual to receive the gold-headed cane presented by Dr. Harold C. Ernst

to the American Association of Pathologists and Bacteriologists to be awarded for special merit.

Dr. Mallory's publications were numerous and covered a wide range of subjects. His first paper appeared in 1892 and his last in 1939. Among his outstanding contributions were studies on the classification of tumors, cirrhosis of the liver, various technical methods and the pathology of infectious diseases. In 1897 he published with J. Homer Wright the first edition of "Pathological Technique" which went through eight editions. A final revision appeared in 1938. "The Principles of Pathologic Histology" was published in 1914.

Aside from his contributions to pathology, Dr. Mallory made a unique contribution to the field of medicine as a whole in the training of young men. The graduates from his laboratory during the period from 1895 to 1932 numbered approximately 125. This does not include graduate students, National Research Fellows or Rockefeller Fellows. He took a keen personal interest in the development, education and welfare of the members of his staff. Even the youngest member had close contact with him and received the benefit of his advice and criticism on every aspect of his work. By such an association, each individual had impressed on him the value of scientific accuracy and a horror of careless technic. The roster of the graduates of the laboratory includes the names of numerous outstanding men, not only in the field of pathology, but also in the clinical branches of medicine. When, in 1933, a special number of the AMERICAL JOURNAL OF PATHOLOGY was issued by the Assistant Editorial Staff in honor of Dr. Mallory, the authors of the included papers were all graduates of his laboratory who had remained in Pathology.

FREDERIC PARKER, JR.

HISTOLOGICAL STUDY OF TROPHIC EFFECTS OF DIABETOGENIC ANTERIOR PITUITARY EXTRACTS AND THEIR RELATION TO THE PATHOGENESIS OF DIABETES *

A. W. Ham, M.B., and R. E. Haist, M.D.

(From the Departments of Anatomy and Physiology, University of Toronto, Toronto, Ontario)

Although the high incidence of diabetes in humans with tumours of the anterior lobe long gave intimation that this lobe of the pituitary gland might possess a diabetogenic function, its rôle in this respect was not definitely established until Houssay and Biasotti [1] in 1930 showed that diabetes, produced in animals by removing the pancreas, could be ameliorated in turn by removing the pituitary gland. Subsequently much information on the relationship between the anterior lobe of the pituitary and diabetes has been obtained by injecting extracts of the anterior lobe into animals. Soon after the experiments of Houssay and Biasotti, three groups of workers produced diabetes in animals by injecting extracts: Evans, Meyer, Simpson and Reichert [2] (1932), Baumann and Marine [3] (1932) and Houssay, Biasotti and Rietti [4] (1932). But, even before Houssay and Biasotti, Johns, O'Mulvenny, Potts and Laughton [5] (1927) had recorded that they had produced hyperglycaemia, glycosuria and polyuria in dogs by the injection of an anterior lobe extract.

The next step in the development of knowledge regarding the relationship of the anterior pituitary to diabetes was of still greater significance to the pathologist. It concerned the discovery that anterior pituitary extracts possess, in addition to their ability to produce a diabetic state during the course of injections, ability to bring about a condition of permanent diabetes associated with islet lesions—a condition which persists indefinitely after the injections are discontinued. The work which led to the establishment of this fact will be briefly reviewed.

In their experiments in 1932, Evans and co-workers [2] observed that two dogs which became diabetic during the course of injections remained diabetic after the injections were discontinued. One recovered after 2 months; the other dog was still excreting

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sugar 4 months after the last injection, when their report was written. The importance of these findings was not generally appreciated until Young [6] in 1937 showed conclusively that a sufficiently severe course of anterior pituitary injections would make an animal diabetic, not only during the injections but indefinitely. Richardson and Young [7] found that this permanently diabetic state was associated with islet lesions.

From the foregoing it is apparent why two terms regarding the conditions caused by anterior pituitary extracts; namely, *temporary* (or transient) diabetes and *permanent* diabetes, have come into use. *Temporary* diabetes refers to the state produced by a less severe course of injections after which recovery is effected when the injections are stopped. *Permanent* diabetes refers to the condition which follows a more severe course of injections and which persists after the injections are discontinued.

Through the courtesy of C. H. Best, in whose department studies on aspects of anterior-pituitary-induced diabetes, other than the histopathology, were being made on a large series of animals, we were able to obtain animals in almost every stage of the condition for pathological study. These dogs were of three series representing (1) almost every stage of temporary diabetes, (2) several stages of recovery from temporary diabetes and (3) permanently diabetic animals.

Temporary Diabetes*

Material and Methods

The animals used in these experiments were dogs of different ages, weights and breeds. The details regarding their treatment, the type of anterior pituitary extract used and the dosage, are given in a separate paper by Best, Campbell and Haist [9] (1939), in which also the results of insulin assays on the pancreases of many of these dogs can be found.

Anterior pituitary extract was given by subcutaneous injection. The first dog was killed 8 hours, and a second 24 hours, after a single injection. Another dog received 3 daily injections, another received 4, 10 received 7 and 4 received 11 daily injections. Twenty-four hours after the last injection, each dog was anaes-

* The material used for a preliminary report [8] is included in this study.

thetized with nembutal, its abdomen opened and the pancreas removed. Blocks less than 3 mm. in thickness were taken from the head, body and tail of the pancreas and fixed immediately in Zenker-formaldehyde solution and in Bouin's solution. The remainder of the pancreas was used for insulin assay. The animals were then killed and autopsies were usually performed within an hour after death, but this was not always possible. Tissue for sections was obtained from the pituitary, thyroid, parathyroid and adrenal glands, and from the liver, kidney and spleen in each case. These blocks were fixed in Zenker-formaldehyde solution. Additional blocks from the liver and kidney of many cases were fixed in formaldehyde for fat stains and in absolute alcohol for glycogen preparations.

Paraffin sections stained with haematoxylin and eosin were prepared from all the organs mentioned. The blocks of pancreatic tissue fixed in Zenker-formaldehyde solution were sectioned in paraffin at 3 μ. Several sets of sections from the three parts of each pancreas were prepared. One set was stained with haematoxylin and eosin, a second by the neutral ethyl violet-Biebrich scarlet method described by Bowie,[10] and a third by the Mallory-azan technique. Other granule stains were occasionally used. Frozen sections of liver were stained with Scharlach R and paraffin sections of the alcohol-fixed liver and kidney were prepared by both iodine and Best's carmine method for the demonstration of glycogen.

Microscopic Findings in Temporary Diabetes

Islets of Langerhans. Islets in the normal pancreas of the dog stained by the Bowie technique after fixation in Zenker-formaldehyde solution did not, in our experience, provide as clear-cut differentiation of alpha and beta cells as did many of our sections stained by the Mallory-azan technique. In the Bowie preparations both alpha and beta granules were blue. The granules of the alpha cells were somewhat larger than those of the beta cells and they were a deeper blue, or even purple. Alpha granules were more tightly packed than beta granules (Fig. 1). Intermingled with the blue granules of the beta cells was a granular, pink to red staining material thought to be cytoplasm rather than specific granules. Beta cells were much more numerous than

alpha cells, some islets being found which, in a single section, revealed no alpha cells; but usually at least a few alpha cells were evident in any single section of an islet. In our experience it was not always possible to decide whether a cell was an alpha or a beta cell. Most cells were clear-cut, but it was difficult to avoid the impression that there were gradations between the two types. We do not infer here that these elements represent one type changing into the other. Throughout this work we were impressed by the fact that the extent of the blue granulation of the beta cells, as estimated by a study of sections stained by the Bowie technique, bore a close relationship to the insulin content of the pancreas in the different animals. (The insulin content was determined and reported by Best, Campbell and Haist,[9] 1939.) The Mallory-azan technique, although excellent for differentiating alpha and beta cells, did not give a very satisfactory indication of the extent of beta cell granulation.

Following injections of anterior pituitary extract the first change observed in the islets was a depletion of beta cell granules. Some depletion was observed after 2 daily injections, greater depletion after 4 injections, and after 7 injections it was extremely difficult to find more than traces of beta cell granules in the sections stained by Bowie's method. The beta cell cytoplasm at this time consisted only of the faint pink to red background described previously (Fig. 2). At this time the alpha granules, except in 2 of the dogs, were still clearly visible in the islets.

The early stages of hydropic degeneration were seen in most of the 10 animals injected for 7 days. In 2 of these the degeneration was well developed, as it was in all but 1 of the 4 animals injected for 11 days. Islands containing hydropic beta cells and unaffected alpha cells were frequently seen in the sections stained with granule stains. No clear-cut hydropic degeneration of alpha cells was observed. In its early stages hydropic degeneration was evidenced by clear vacuoles in the cytoplasm of the beta cells. In more advanced stages the cells became swollen with fluid and the cytoplasm reduced to a lacy network extending from the nucleus to the cell membrane. In advanced stages the nucleus tended to be pyknotic and the cytoplasm to be almost completely replaced with fluid (Fig. 3).

The alpha cells appeared to be unaffected in all animals ex-

cept the 2 in which severe hydropic degeneration of beta cells occurred after 7 daily injections of the extract. In 1 of these there was a complete lack of alpha granules and in the other a moderate degree of alpha cell degranulation. The islets in these animals were surrounded by acinar tissue in which the fixation and staining were excellent, hence the lack of alpha cell granules could not be attributed to faulty fixation or staining. These 2 animals in which alpha cells evidenced degranulation were the only ones in which there was an extensive deposition of fat in the liver.

Mitotic figures appeared in the islets (Figs. 5, 6 and 10) as soon as 4 days after the first injection; and up to 11 days were not uncommon. On occasion two were detected in the same islet (Fig. 5). From the haematoxylin and eosin sections the mitotic figures appeared to be in beta cells.

Acini. Mitotic figures were seen in acini as soon as 3 days after injections were begun. They were numerous at 7 days (Figs. 7, 9 and 10) and were still apparent after 11 daily injections. Two mitotic figures in the same oil-immersion field were very commonly found and it was not unusual to find three (Fig. 9).

Ducts. No alterations were observed in the larger ducts. Mitotic figures were found in the smaller ducts (Fig. 8). The small ducts in some of the 7-day animals demonstrated clear vacuoles in the cytoplasm of their cells. This condition was more pronounced in the 7-day animals (Fig. 4).

Undifferentiated Duct Epithelium. Bensley [11] described cords and tubules of undifferentiated epithelium which connect with both islets and ducts in the pancreas. On many occasions, cells were seen between acini which we interpreted as belonging to this system. These cells did not contain the specific granules of the islet cells, but single alpha and beta cells were frequently seen in identical situations, suggesting that they had developed from the undifferentiated cells. Without employing quantitative methods it was impossible to establish whether the injections of the extract led to an increase in the number of beta or alpha cells in these locations, or whether the number of undifferentiated cells was greatly increased. Mitotic figures were observed in the latter (Fig. 11), as well as vacuolation (Fig. 4) similar to that seen in the ducts.

Thyroid Gland. Up to 7 days after the beginning of daily injections the follicular cells gradually increased in size and became columnar in shape (Fig. 13). In many of them a vacuolated, light-staining area appeared between the nucleus and the inner cell border. Mitotic figures were common from the third to the seventh day (Fig. 14). Infolding of the walls of the follicles developed in some of the animals between the fourth and seventh days. Up to the seventh day the amount of colloid was gradually reduced and a well marked zone of vacuoles became apparent between the remaining colloid and the inner border of the follicular cells. The colloid stained much less intensely with eosin. After 11 daily injections the histological changes in the thyroid were not so great as in some of the 7-day animals.

Parathyroid Glands. In the parathyroid glands the chief alteration was the proliferation of cells. In the interval between the third and seventh daily injections, mitotic figures were readily observed (Fig. 16). As many as three were found in a single oil-immersion field. Two mitotic figures in the same oil-immersion field were found in many sections. The cytoplasmic changes were not marked. As may be seen in Figure 16, the nuclei in some areas were separated somewhat further from one another by a lighter staining cytoplasm than is normally the case.

Adrenal Cortex. Even though allowing for the fact that it is difficult to ensure that sections of different adrenals are cut at comparable sites and in the same plane, there was considerable variation in the microscopic appearance of the adrenals in animals similarly treated. On the whole, the most marked alteration was in the zona glomerulosa. In the dog this zone is normally of considerable depth and is composed of cells which have paler cytoplasm than those of the adjoining zona fasciculata (Fig. 17). An appreciable number of mitotic figures were found in the zona glomerulosa after 2 daily injections of the extract. In other animals which received up to 7 injections the number of mitotic figures varied considerably but on the whole they were numerous between 4 and 7 days (Fig. 19). It was not unusual to see two in a single oil-immersion field. The cytoplasm of the cells of the zona glomerulosa became increasingly vacuolated up to 7 daily injections and the cells were larger. The depth of the zone was increased (Fig. 18).

The zona fasciculata was affected to some degree by the extract. Occasional mitotic figures were observed in this region.

Liver. After 1 and 2 injections of the extract, the parenchymal cells were evenly vacuolated to a moderate degree. The carmine and iodine preparations indicated that vacuolation was due to glycogen. After 3 injections of the extract, the parenchymal cells close to the central veins became extensively vacuolated (Fig. 20). After 7 daily injections, areas of the parenchyma were seen in which the constituent cells were greatly swollen with fluid (Figs. 21 and 22). Little cytoplasm was apparent in these cells. Many of them had pyknotic nuclei which were located at the side of the swollen cell. In some cases cell boundaries were broken. In preparations stained by Best's carmine and iodine methods, glycogen was shown to be present in the fluid content of the cells and a few intercellular pools of fluid containing glycogen were scattered about in these areas of swollen cells. In some livers fluid which was stained by the glycogen stains was present in distended portal lymphatics. The sinusoids were apparently obliterated in the areas where the liver cells were swollen. The histological picture in these areas of swollen liver cells presented a striking resemblance to that of the liver in von Gierke's disease observed by Boyd.[12]

After 11 daily injections, the livers of the animals we examined did not present such extensive vacuolation as those of the 7-day animals. In one 11-day animal there were a great many mitotic figures present in the liver.

In two 5-day animals the parenchymal cells of the liver were loaded with fat droplets (Fig. 15). The fat was widely distributed throughout the lobules and each cell contained many droplets. These two livers contained little glycogen. Apart from these 2 animals the fat stains revealed little fat in the livers of the injected animals. The 2 dogs which showed extensive deposition of liver fat were the only ones in which the alpha cells of the islets had been noticeably affected.

Kidney. Several kidney sections were stained for glycogen but only a little was seen in one 7-day animal. Mitotic figures were observed in the loops of Henle in 1 of the animals injected for 11 days.

Recovery from Temporary Diabetes

Material and Methods

This group consisted of 6 animals which were injected once daily for 7 days and then allowed to recover for 2, 3, 4, 5, 8 and 27 days respectively before they were sacrificed.

The methods employed in this experiment were similar to those described under the heading "Temporary Diabetes."

Microscopic Findings

In the dog sacrificed 2 days after receiving the last of 7 daily injections, the histological picture in various organs differed little from that observed 1 day after 7 daily injections (Fig. 23).

Three days after the last of 7 daily injections, preparations of the pancreas stained by the Bowie method for the first time in this series revealed some well granulated beta cells and some which contained varying degrees of granulation up to normal (Fig. 24). The latter cells gave the impression that the beta granules were somewhat larger and more intensely stained than usual. Some areas in islets at this time demonstrated no beta granulation. The alpha cells were numerous and well granulated. In preparations stained by haematoxylin and eosin, mitotic figures were still seen in the acinar cells of the pancreas but, for the first time in this series, no hydropic degeneration of islet or duct cells was observed. No mitotic figures were observed in the adrenal cortex. The liver cells had somewhat more than a normal content of glycogen and presented a normal appearance. The colloid in the thyroid follicles was more deeply stained than hitherto. The follicles were not completely filled, however, and the epithelium was columnar. One mitotic figure was seen in the section of the parathyroid gland.

Four days after the last of 7 daily injections of the extract, pancreatic tissue prepared by the Bowie method revealed a normal extent of granulation in the beta cells (Fig. 25). The granules, however, seemed to be somewhat larger and darker than usual. In the haematoxylin and eosin preparations, occasional mitotic figures were found in the acinar cells of the pancreas. The thyroid epithelium was still high but the colloid was deep

pink. The adrenal gave no histological indication of heightened activity.

Five days after the last of 7 daily injections, the thyroid epithelium was still higher than normal and some mitotic figures were found in the adrenal cortex. Other tissues evidenced no abnormalities.

Eight days after the seventh daily injection, the thyroid gland demonstrated follicles lined by cuboidal epithelium and well filled with deep pink colloid. The liver contained a large amount of glycogen.

Twenty-seven days after the seventh daily injection, the various endocrine glands examined presented pictures within the range of normality. The islets of Langerhans, however, exhibited slightly more collagen in association with their vessels than usual.

Permanent Diabetes

Material and Methods

Tissue was obtained at operation from the head, body and tail of the pancreases of 3 dogs. It was fixed in Zenker-formaldehyde and Bouin's solutions. Sections were prepared by the same technique as described under the heading "Temporary Diabetes."

One dog received daily intraperitoneal injections of an anterior pituitary extract for 21 days and the other 2, for 30 days. Administration of insulin was started 30 to 59 days after the last injection of the extract. Tissue was obtained at periods ranging from 78 to 198 days after the last injection of anterior pituitary extract. Best, Campbell and Haist [9] have reported that these 3 dogs were permanently diabetic and that their pancreases contained little insulin.

Microscopic Findings

The three pancreases exhibited one feature in common, a lack of granular beta cells. Aside from this fact the three pancreases differed considerably in their microscopic appearance.

Sections of the first pancreas, stained by haematoxylin and eosin, revealed no typical islets. Only small groups of fibroblasts,

which bore only a superficial appearance to islets, were found (Fig. 28). The Bowie preparations of this pancreas revealed only occasional islet cells scattered through the acinar tissue. The granules in these cells resembled those of alpha cells. The Mallory-azan preparations showed increased connective tissue, which had a diffuse distribution. The acinar tissue was somewhat atrophic in appearance and the smaller ducts were not as prominent as usual.

The second pancreas revealed islets which in the haematoxylin and eosin preparations appeared almost normal. They were not present, however, in nearly as great numbers as in a normal pancreas. Granule stains revealed that these islets consisted chiefly of alpha cells (Figs. 26 and 27). There was a marked scarcity of granular beta cells in this pancreas. From Mallory-azan preparations it was found that a slight diffuse fibrosis was present and that the islets had more collagen about their blood vessels than was usual. The acinar tissue appeared to be normal.

The third pancreas was removed from a permanently diabetic animal which had been hypophysectomized a few weeks before autopsy. Histological examination of the brain revealed, however, that the hypophysectomy was not complete, as a small area of anterior lobe tissue was found in the serial sections. Sections of the pancreas of this animal, stained by haematoxylin and eosin, showed a slight to moderate diffuse fibrosis. Islets were seen but they were not as numerous as in a normal pancreas. Some hydropic cells were present in the islets. Granule stains revealed few granular beta cells in the islets and many alpha cells. The most striking finding in this pancreas was the extensive hydropic change in the cells of the smaller ducts. This change was not present in the pancreases of the other two permanently diabetic animals.

Discussion

The Histological Basis for "Permanent" Diabetes

Richardson and Young [7] were the first to make histological studies on animals made permanently diabetic by anterior pituitary injections. In 1938 they reported their findings in the pancreatic tissue of 2 permanently diabetic dogs. Next, the pancreas of a permanently diabetic dog prepared by Campbell and Best [18]

(1938) was studied by both Robinson and Warren, their findings being briefly reported in the paper by Campbell and Best. Warren [14] has also independently discussed this tissue and the tissue from 2 of Young's dogs. Dohan and Lukens [15] have published a brief report on the histological findings in the pancreases of 2 permanently diabetic dogs and Richardson [16] has recently given data on 3 more.

The various pancreases examined by these workers and the three in our own series have one point in common, namely, a scarcity of islets. Granule stains used by Richardson [16] and also in the present study indicate, furthermore, that the scarcity of granular beta cells is even more pronounced than the scarcity of islets.

In other respects the various pancreases which have been studied differ from one another. For instance, Richardson [16] appears to have found a greater incidence of hyalinization of islets than has been observed in the others, as well as more examples of duct vacuolation. We are inclined to agree with Richardson's view that vacuolation of the smaller ducts is the most characteristic finding in the pancreas after anterior pituitary extracts are injected, but we base our conclusions on our findings in temporary diabetes. After the injections had ceased we found duct vacuolation to be less common. It was present in only one of the three pancreases examined by us. Hydropic degeneration of islets was observed in only a few of the pancreases studied by Richardson. It was evident in the pancreas of the first dog made permanently diabetic by Campbell and Best [13] and it appeared in only 1 of the 3 dogs we studied. Like the vacuolation of the smaller ducts, however, we found that hydropic degeneration was characteristic of a certain phase of temporary diabetes, rather than of permanent diabetes. We suspect that its absence in permanent diabetes may be due to an absence of beta cells capable of becoming hydropic. The amount of diffuse fibrosis in the various pancreases studied seemed to vary considerably. We gained the impression that in association with it there was atrophy of the smaller ducts.

To sum up, the pancreases obtained from dogs made permanently diabetic with anterior pituitary extracts revealed a scarcity of islets. With granule stains it has been evident that the lack

of granular beta cells was almost complete. Hence it seems reasonable, for the time being, to adopt the position that permanent diabetes is due to a lack of insulin production. Why anterior pituitary extracts should bring about this state of affairs will be discussed next, in the light of our findings in temporary diabetes.

The Cause of the Diabetic State in Temporary Diabetes

Unlike permanent diabetes, temporary diabetes cannot be explained by the single factor of an absolute reduction in insulin production.

We found that daily injections of anterior pituitary extract produced a progressive degranulation of the beta cells and that this change was closely followed by hydropic degeneration. Our findings in pituitary-injected animals are identical with those observed years ago by Homans [17] and Allen [18] in pancreatic remnants, when enough of the pancreas had been removed to cause diabetes. In his long series of experiments, Allen offered convincing evidence that hydropic degeneration of the beta cells in the partially depancreatized animal was caused by their being called on to perform work beyond their capacity. Since the changes we observed in animals injected with anterior pituitary extracts so closely resembled those he found in the partially depancreatized animal and as they developed in the same sequence, we conclude that they result from the same cause, namely, excessive stimulation of activity. Hence we suggest that the reason anterior pituitary extracts can cause islet damage is because of their ability somehow to stimulate beta cells to overwork.

To attribute the beta cell lesions that we observed to overwork has interesting implications. First, from Allen's [18] work in partially depancreatized animals, it seems clear that hydropic degeneration does not develop until beta cells are called on to perform many times their usual amount of work. For example, removing two-thirds of the pancreas does not result in hydropic degeneration in the remaining fragment; for this to occur four-fifths to nine-tenths of the pancreas must be removed. It would appear from this that beta cells must be called on to perform five to ten times their normal work before they show hydropic degeneration. Hence in our dogs in which, in contrast to the

partially depancreatized animal, the whole pancreas was present, it might be concluded that before widespread hydropic degeneration appeared the total insulin liberation of each pancreas was many times the normal amount. It is necessary, therefore, to explain why this greatly increased insulin output was not associated with a great reduction in the blood-sugar level but instead with a slight elevation in the blood-sugar level during the first few days of injections (for blood sugar curve see Best, Campbell and Haist [9]).

To answer this question we refer again to the work of Houssay and his associates.[1,4] When they discovered that diabetes resulting from pancreatectomy was ameliorated by hypophysectomy, they laid the basis for the conception of diabetes as a disease due to a disturbed relationship between anterior pituitary and beta cell activities rather than as one which results when insulin production falls below a certain absolute minimum. To carry this thought a little further, if the absence of diabetes depends upon the constancy of the ratio,

$$\frac{\text{diabetogenic activities of (or controlled by) anterior pituitary}}{\text{antidiabetogenic activity of beta cells (insulin secretion)}},$$

then diabetes could be seen to be present or absent over a wide range of absolute values for the two factors in the ratio. In the case of the animals in the early stages of temporary diabetes, both factors were generally increased. But because of the great increase in the numerator, the increased denominator (insulin secretion) was not effective in bringing about hypoglycaemia. Indeed, at best it was only able approximately to balance the increased numerator for a few days, after which it became unable to compensate further for the increased numerator and the diabetes became greatly accentuated.

The Cause of the Excessive Stimulation of Beta Cells Observed After the Injection of Anterior Pituitary Extract

There are two ways in which anterior pituitary extracts could stimulate beta cells: *indirectly* and *directly*. The *indirect* method would depend on effects of the extract exerted elsewhere than the pancreas, which increase the need of the organism for insulin. The *direct* method would depend on the existence in the extract of a principle which directly stimulates beta cell secretion. From

our studies it seems reasonable to conclude that beta cells were stimulated by both methods.

1. Indirect Stimulation. One anterior pituitary effect which would indirectly stimulate beta cells by creating increased need for insulin is the effect on the thyroid. The histological picture in this gland indicated that under the influence of the injected anterior pituitary extract it became extremely active. The state of hyperthyroidism caused by the extract would have a definite effect on increasing the need for insulin.

A second effect of the extract which would indirectly stimulate beta cell activity by increasing insulin need was observed in the adrenal cortex. Here, as in the thyroid, the histological picture indicated great functional activity (Figs. 18 and 19). Long, Lukens and their associates [19] have offered much evidence which indicates that the cortical hormone stimulates the formation of sugar from protein. Such an effect would increase the body's need for insulin.

A third effect of the extract was observed in the liver. Houssay [20] stated that the liver is the only organ in the body, the removal of which will prevent the diabetogenic effects of anterior pituitary extracts. In this work we have described a characteristic liver lesion which developed when the extract was given in daily injections. This lesion consisted essentially of a hydropic state of the liver cells, associated with loss of their granular cytoplasm. The fluid in these distended cells contained glycogen. Warren [14] stated that some of the larger livers he had studied in human diabetes suggested hydrops of the liver cells. The histological picture of the liver cells in the lesions we observed closely resemble those in the liver of a case of von Gierke's disease illustrated by Boyd. [12]

As far as could be judged by our glycogen stains, the glycogen content of the liver, which was excellent at the beginning of the experiment, altered only to become slightly increased as the injections continued. As the liver was on a positive glycogen balance, some of the extra glucose in the blood must have been derived from other than carbohydrate sources, probably from protein. The manufacture of sugar from materials other than carbohydrate takes place in the liver and it is possible that the peculiar hydropic state of many of the liver cells is related to

their activity in making sugar from noncarbohydrate materials. This activity of the liver cells may not be due solely to the direct action of an anterior pituitary principle.*

One result of the described effects of the anterior pituitary extract would be to increase the sugar which the body must metabolize (sugar from protein and possibly from fat). Hence if insulin is needed for the metabolism of carbohydrate, this effect would increase the body's insulin requirements.

However, it appears probable that anterior pituitary extract increases insulin need in an additional way concerned with rendering insulin ineffective. Many workers have shown that shortly after receiving anterior pituitary injections animals exhibit a reduced response to injected insulin despite the fact that the blood sugar is not yet elevated (Houssay and Potick,[21] Cope and Marks [22]). If insulin secretion is controlled by the blood-sugar level, the insulin resistance observed by these workers would not place any increased strain on the beta cells since the blood-sugar level was not raised in their experiments. It would place a strain on the beta cells, however, if insulin secretion is controlled by the level of insulin in the blood. In support of this method of control, we found that beta cell secretion, as indicated by the state of granulation, was greatly stimulated in the early phases of temporary diabetes at a time when the fasting blood-sugar levels were not high. Furthermore, Allen [23] showed that partially depancreatized phloridzinized dogs developed the typical islet cell lesions as readily as partially depancreatized dogs not given phloridzine, despite the fact that the blood sugar was not elevated. It would appear, therefore, that beta cells can be strained in the absence of a diabetic blood-sugar level. The evidence suggests that insulin secretion may be controlled primarily by the blood-insulin level. This cannot be definitely established until methods of measuring the blood-insulin level are available. If insulin secretion is controlled by the blood-insulin level, it is easy to see that any anterior pituitary effect which acts to metabolize insulin would lower the blood-insulin level and stimulate beta cell secretion.

* The work of Long and his associates [19] suggests that the hormone of the adrenal cortex is involved in this effect also, but Houssay [20] and his co-workers offer evidence in some of their experiments that the effect can be produced in the absence of the adrenals.

2. Direct Stimulation. It seems advisable to point out that there is no clear-cut concept of what constitutes a "trophic" effect. The word refers to nutrition and has been applied to growth. However, it is obvious that secretion, as well as growth, is stimulated by many, if not all, of the so-called "trophic" principles present in anterior pituitary extracts. For instance, loss of colloid is one of the characteristic effects of the thyrotropic principle on the thyroid gland (Fig. 13). The two phenomena, of increased secretion and growth, parallel each other in so many endocrine glands stimulated by the injection of "trophic" principles that it seems unwise, until further information is obtained, to visualize these principles as stimulating only growth. As to growth and secretion, it appears more probable that an action primarily affecting secretion would be more likely to induce growth than *vice versa.* Much more information is needed on this important subject, but from our findings in most of the endocrine glands we wish to emphasize the secretory effect of the pituitary principles in addition to their proliferative actions.

In 1933 Anselmino, Herold and Hoffmann,[24] described an anterior pituitary extract which on injection into rats led to an increase in islet tissue. (Anterior pituitary extracts do not cause diabetes in rodents unless part of the pancreas is removed. There is a marked difference among species with regard to their response to the same extract.) Some workers have confirmed and others have failed to reproduce their results, but Richardson and Young [25] have shown that crude preparations of anterior pituitary extract will lead to an increase in the weight of the pancreas and to an increase in islet tissue. Recently, Marks and Young [26] have shown that repeated injections of an anterior pituitary extract will lead to an increase in the insulin content of the pancreas of the rat.

We have pointed out that anterior pituitary extracts induce growth in all parts of the pancreas. (Figs. 5-11 illustrate these growth effects.) But we question whether growth is the only change brought about by the action of the pancreatropic principle in the dog. If it is like other trophic principles which affect endocrine glands, it would stimulate secretion as well. So, although excess secretory function of beta cells in the pituitary-injected animals can be explained, in part at least, by an attempt to pro-

vide for the increased need for insulin, we think that direct stimulation of secretory activity by the pancreatropic principle may be an important factor in causing the exhaustion of beta cells. It was our impression from the various endocrine glands studied, that trophic principles act by removing restraints on endocrine gland-cells which ordinarily hold their secretory and growth activities within certain limits. This is not a permanent effect as we found that trophic stimulation usually became less effective as injections continued. After a certain amount of trophic stimulation, the cells in most glands resumed a more normal appearance. But in the effective phase of trophic stimulation conditions might permit cells to attempt work beyond their physiological limits. In the absence of trophic stimulation it seems doubtful that a few days of ordinary overwork would produce the profound islet lesions observed. Hence it seems possible that trophic stimulation of beta cells may be a factor in causing or permitting the excessive overwork which leads to their exhaustion.

The Relation of the Injected Extract to the Alpha Cells and Liver Fat

The alpha cells of the islets appeared much more immune to the effects of the extract than the beta cells. In only 1 animal was there an almost complete degranulation of alpha cells. This animal showed extensive depositions of fat in the liver. The only other fatty liver in the series was obtained from an animal which showed a moderate degranulation of alpha cells. The coexistence of fatty livers and alpha cell degranulation in these 2 animals may be only a coincidence, but because of the recent interest in the relation of the pancreas and anterior pituitary to fat metabolism it merits mention.

Possible Types of Diabetes and their Relation to Islet Lesions

That pancreatectomy produces diabetes, that islet lesions are found in many human cases of diabetes and that insulin relieves diabetes have encouraged the view that diabetes is a disease due to an absolute reduction in insulin production. But the equally impressive fact that a large percentage of humans with diabetes demonstrate no islet lesions at autopsy has always stood in the

way of the unquestioning adoption of this concept. The relatively recent work in connection with the anterior pituitary and diabetes has led to the development of a somewhat different concept of the cause of the disease and may give some intimation why some cases exhibit islet lesions while others do not.

Sufficient evidence has been presented in this paper to show that diabetes may be due not to a simple reduction in insulin liberation but rather to an increase in the $\frac{\text{insulin needs}}{\text{insulin production}}$ ratio. An increase in the ratio, and hence diabetes, is theoretically possible, because of (1) a decrease in insulin production and liberation below needs, or (2) an increase in needs beyond production and liberation of insulin. Thus it is theoretically possible that diabetes could result primarily from either *pancreatic* or *extrapancreatic* causes. For example, temporary diabetes produced by extracts is, in its early phases, extrapancreatic diabetes because it depends primarily on insulin needs being increased. Permanent diabetes is, however, pancreatic diabetes as there is islet damage and decreased liberation of insulin.

Our work shows how diabetes resulting from increased insulin needs (extrapancreatic diabetes) can terminate as pancreatic diabetes with islet lesions. This is due to beta cells endeavouring to balance the $\frac{\text{insulin needs}}{\text{insulin production}}$ ratio whenever needs are increased. In the animals studied, very large amounts of extract were injected and the needs were enormously increased. Furthermore, there was evidence of considerable pancreatropic effect of the extract, which we think may be an important factor in permitting gross overwork of the beta cells. It is conceivable that conditions might arise in man which would lead to an increase in insulin needs but with which there would be no undue secretion of pancreatropic principle and hence no exhaustive overwork of beta cells.

It is too soon to be certain why some humans with diabetes show no islet lesions. First, pancreatic tissue from more human cases with apparently normal islets needs to be investigated by means of granule stains to make sure these apparently normal islets are not constituted almost entirely of alpha cells or agranular beta cells, as in permanent diabetes in dogs. Second, it is

possible that there is a condition, as yet not understood, in which insulin is somehow prevented from exerting its action, without being metabolized, so that it remains in the circulation and inhibits secretion by the beta cells which are therefore undamaged. Third, humans with diabetes who show no islet lesions may possibly be those in whom the condition is primarily due to increased insulin needs but in whom the factors necessary to produce exhaustive overwork of beta cells are lacking (*e.g.*, enough of the pancreatropic factor or a poor beta cell potentiality).

Whether it is possible to distinguish clinically between diabetes due primarily to increased insulin needs and that due primarily to diminished insulin production is a matter outside the scope of this paper. Himsworth [27] and Graham [28] have recently discussed the problem of two clinical types of human diabetes and the problems arising therefrom.

Beta Cell Regeneration

It is useless to speculate at present whether the islet lesions evident in most cases of diabetes are due to the beta cells attempting to compensate for unusual insulin needs or to their inability to compensate for ordinary needs. In any case, beta cell potentiality must be equivalent to the insulin needs of the individual if diabetes is to be absent. It seems desirable, therefore, to comment briefly on the problem of beta cell regeneration, particularly as we have obtained some evidence to indicate a vicious circle, in that, beyond a certain point, extra work put upon beta cells operates to prevent their new formation.

Our results indicate that the islets can recover after a few days of severe diabetes. Degranulated beta cells recovered their granules in 3 days and even moderately hydropic cells recovered, so far as we could tell. But in the dog, if frank diabetes can be prolonged by continuing the injections, the animal becomes permanently diabetic due, we presume, to beta cells being injured beyond the point of recovery. Recovery of function of the pancreas after this depends upon the formation of new beta cells.

When, because of overwork, the beta cells are injured beyond the point of possible recovery, regeneration of new beta cells becomes unusually difficult. The injured beta cells are certainly

not a good source of new cells. What is perhaps even more important is that stem cells—those of the smaller ducts and cords of undifferentiated epithelial cells—also become hydropic. That the stem cells become vacuolated as well as the functioning differentiated beta cells, may be an important reason why a diabetic condition tends to persist. (Allen [18] observed duct vacuolation after partial pancreatectomy and stressed its importance in inhibiting the formation of new islets. Richardson,[16] as well as ourselves, has observed it after anterior pituitary injections and stresses its importance with regard to islet regeneration).

It is readily apparent that for untreated pancreatic diabetes each new beta cell which the pancreas manages to produce would be overworked and probably destroyed as soon as it develops. It might be thought that this could be prevented by giving insulin, but it is possible that supplying adequate amounts of exogenous insulin may remove, to a great degree, the stimulus for beta cell regeneration. Successful beta cell regeneration seems to require a stimulus for regeneration without excessive strain on any newly formed beta cells. An attempt to obtain these two requirements was recently made by Campbell, Haist, Ham and Best,[29] who, in a preliminary report, stated that the administration of insulin with anterior pituitary extract prevented, to a considerable degree, the development of degenerative changes in beta cells; yet the production of new islet cells, as witnessed by mitotic figures, was still observed.

Whether the potentiality for beta cell formation is lost in the pancreas of a dog which has suffered for some time from the permanent type of diabetes, is an important question. If this potentiality is not lost and if experimental means can be found to stimulate the formation of new beta cells without causing their subsequent overwork, there would be hope of its application in the treatment of human diabetes. It is a great advance that animals can be made permanently diabetic, for this provides suitable experimental material for study. But, until it can be shown that anterior pituitary extracts can cause new beta cells to form in a permanently diabetic animal, it would be unwise to regard the pancreatropic effect of anterior pituitary extracts, observed in previously normal animals, as the answer to beta cell regeneration. The smaller ducts in the pancreases of 2 of the

permanently diabetic animals which we studied appeared atrophic as compared to normal ducts. It is possible that after a long period of unproductive stimulation from the animal's own pituitary gland, the character and potentiality of these stem cells might alter.

We do not believe that new beta cells can form from fully differentiated acinar cells, despite the recent support this theory has received from Woerner,[30] Sergeyeva [31] and Richardson.[16] Bensley [11] reviewed this problem several years ago. He found no convincing evidence that acinar cells could form islet cells and postulated certain criteria which would have to be satisfied before such a premise could be granted. One set of requirements was that cells should be found which contained the granules of both acinar and islet cells. These requirements have been met, according to Woerner, Sergeyeva and Richardson. We too, in this study, occasionally observed cells which appeared to fulfill these requirements, but it is very difficult to be certain about observations of this nature. Even if such cells exist in the pancreas, we think that they offer no evidence with regard to acinar cells becoming islet cells or *vice versa*. From studies made by one of us [32] on the formation of cartilage and bone, it became apparent that when stem cells exist and retain equal potentiality for differentiating into two end-products, the path which differentiation takes depends upon environment. When the environmental influence is not clear-cut, the stem cells differentiate along a middle course and produce tissues having the characteristics of both of the usual end-products. Hence we regard these cells with the characteristics of both acinar and islet cells as nothing more than an indication that stem cells in this case differentiated in a complex environment. Gradation tissues, in our opinion, indicate metamorphosis only when they exist between a series of cells in progressive stages of differentiation. We consider acinar cells and beta cells both as highly differentiated elements.

Summary

Histological studies were made on the organs of a large number of dogs made diabetic with an anterior pituitary extract by Best, Campbell and Haist, who have reported on aspects of diabetes in these dogs other than the histopathology.

Daily injections of this extract led to a progressive degranulation of the beta cells of the islets of Langerhans. This was usually almost complete after 7 daily injections. The later stages of degranulation were associated with the development of hydropic degeneration of the beta cells which became very extensive immediately following degranulation. The cells of the smaller ducts and cords of undifferentiated epithelium also became hydropic.

During the first 7 days of injections, hypertrophy, hyperplasia and cytoplasmic changes indicative of increased secretory activity developed in the cells of the thyroid gland, the parathyroid gland and the adrenal cortex. During this same period many mitotic figures were observed in the cells of pancreatic acini, in the cells of the small ducts of the pancreas and in the cords of epithelial cells of the pancreas. Before hydropic degeneration was severe, mitotic figures were also seen in pancreatic islets.

After 3 daily injections of extract most injected animals showed areas of hydropic liver cells. In these cells the granular cytoplasm was depleted and the cells were swollen with fluid which contained considerable glycogen. In some animals injected for 7 days, more than one-half of the liver cells were affected in this manner. Most of the livers of the injected animals demonstrated very little fat in frozen sections. In 2 animals injected for 5 and 7 days, the livers were very fatty. In 1 of these animals the alpha cells of the pancreas were degranulated; in the other animal the pancreas evidenced some depletion of alpha granules but degranulation was not complete. In all other animals the alpha cells were well granulated.

In a series of animals allowed to recover after receiving 7 daily injections of extract, the beta cells had recovered about one-half of their granules 3 days after the last injection. Four days after the last injection granulation was complete. Three days after the last injection, recovery had occurred from such hydropic degeneration as was present after 7 daily injections. The connective tissue of the islets was increased in animals which recovered after receiving 7 daily injections of extract.

In 3 animals which were injected with daily doses of extract for 21 to 30 days and from which pancreases were obtained months later there was a scarcity of islets and a lack of granular beta cells.

In all animals, the extent of beta cell granulation as depicted by the Bowie technique, closely paralleled the insulin concentration in the pancreas as reported by Best, Campbell and Haist.

Conclusions

1. Anterior pituitary extracts, injected in daily doses into dogs, cause progressively, degranulation, hydropic degeneration and death of the beta cells by stimulating these cells to excessive function.

2. Anterior pituitary extracts may act in two general ways to cause beta cells to overwork:

(a) By acting on tissues and organs other than the pancreas so as to increase the body's need for insulin. Such actions include increasing the amount of carbohydrate to be metabolized, and also making insulin relatively ineffective.

(b) By exerting a "trophic" effect on the pancreas. This is indicated by proliferative changes (mitotic figures in various epithelial elements, including the beta cells). It may also be a factor in permitting the beta cells to secrete at a destructively high rate, since trophic principles in general seem to affect secretion as well as growth.

3. Diabetes is seen to be due, not to a decrease in a fixed production of insulin, but rather to an increase in the $\frac{\text{insulin needs}}{\text{insulin production}}$ ratio.

4. The early stages of diabetes produced by anterior pituitary extracts can be explained primarily by increased needs for insulin.

5. The later stages of diabetes produced by extracts (permanent diabetes) can be explained primarily by diminished production of insulin.

6. It is evident that, experimentally at least, there are two general types of diabetes: one due primarily to increased insulin needs, the other primarily to decreased insulin production. It is also evident that diabetes due primarily to increased needs may lead to exhaustion of beta cells and hence decreased production.

7. Beta cells, stimulated to excessive activity for only a few days, will recover if the injections of extract are discontinued,

but will not recover when stimulated to excessive activity for a sufficiently long time.

8. That the cells of the smaller ducts and cords of undifferentiated epithelial cells in the pancreas become hydropic during the course of injections is considered to be an important factor in a vicious circle which operates to interfere with an adequate regeneration of beta cells once diabetes is established.

NOTE: We wish to express our appreciation to C. H. Best for suggesting that this study be made and for his courtesy in providing the animals used.

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DESCRIPTION OF PLATES

PLATE 124

FIG. 1. Oil-immersion photomicrograph of an islet in a Bowie preparation of pancreas obtained from a dog which received 1 injection of extract 8 hours before it was killed. Two alpha cells can be seen on the left side of the islet, recognizable by their dark granules. The other dark-staining material slightly below the center of the islet is a capillary and its supporting reticulum. The remainder of the cells in the islet are beta cells and their fine granulation is apparent.

FIG. 2. Oil-immersion photomicrograph of an islet in a Bowie preparation of pancreas obtained from a dog which received 7 daily injections of the extract. Acinar cells with zymogen granules mark the left border of the islet. Close to the center some alpha cells, well filled with their coarse, dark granules, are apparent. The remainder of the cells in the islet are beta cells. Their blue granulation has almost completely disappeared; nothing remains but the pale cytoplasmic background. Some of the beta cells are hydropic.

FIG. 3. Islet from a dog which received 11 daily injections of the extract. The preparation is stained with haematoxylin and eosin. Many of the islet cells are hydropic.

FIG. 4. Medium power photomicrograph of an area of pancreas obtained from a dog which received 7 daily injections of the extract. The section is stained with haematoxylin and eosin. Hydropic degeneration is evident in several islets and in smaller ducts and cords of undifferentiated epithelial cells. Continuity of an islet and a small duct is obvious in one instance.

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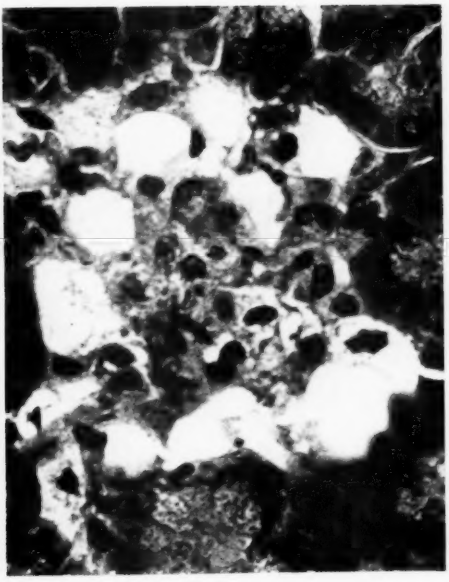

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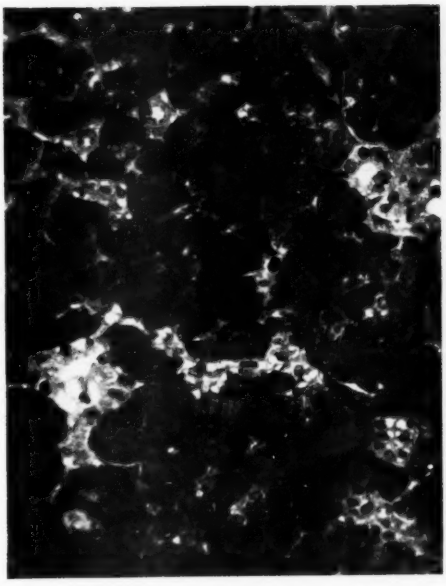

4

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Histopathogenesis of Diabetes

PLATE 125

FIGURES 5 to 11 inclusive illustrate the pancreatropic effect of the extract.

FIG. 5. Oil-immersion photomicrograph of a section stained by haematoxylin and eosin from a pancreas obtained from a dog which had received 4 daily injections of the extract. Two mitotic figures are present in this islet: one in the midline close to the border of the acinar tissue; the second above it, is close to the apparent centre of the islet.

FIG. 6. Preparation same as for Figure 5 showing mitotic figure in islet.

FIG. 7. Preparation same as for Figure 5 showing two mitotic figures in acinar cells.

FIG. 8. Preparation same as for Figure 5 showing mitotic figure in cell of small duct.

FIG. 9. Preparation same as for Figure 5 showing three mitotic figures in acinar cells in the same oil immersion field.

FIG. 10. Preparation same as for Figure 5 showing one mitotic figure in islet above, and one in acinar cell below.

FIG. 11. Preparation same as for Figure 5 showing two mitotic figures in a cord of undifferentiated epithelium in the centre of the field.

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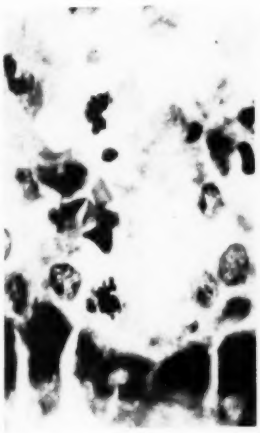

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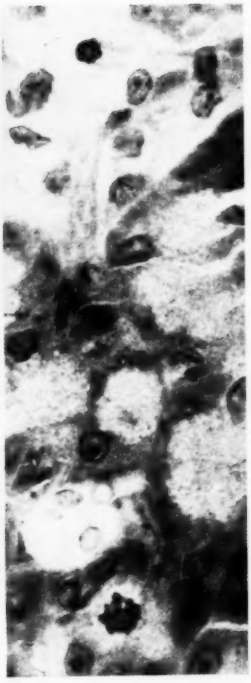

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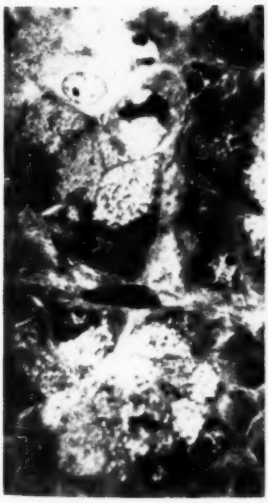

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11

Ham and Haist

Histopathogenesis of Diabetes

Plate 126

Fig. 12. High power photomicrograph of thyroid gland from a control dog. haematoxylin and eosin stain.

Fig. 13. Medium power photomicrograph of thyroid gland from a dog which received 4 daily injections of the extract. A loss of colloid, heightened epithelium and infolding of follicular walls are apparent. This illustrates the thyrotropic effect of the extract.

Fig. 14. Oil-immersion photomicrograph showing mitotic figure in the same preparation as used for Figure 13.

Fig. 15. Low power photomicrograph of frozen section of liver obtained from one of the two atypical animals which received 5 daily injections of the extract. The preparation was stained with Scharlach R. The liver cells contain large numbers of fat globules which are dark in the photograph. The fat in the epithelium of the bile ducts is also apparent. (This is normal in the larger ducts.) In this animal there was degranulation of the alpha cells of the pancreas. This picture illustrates the probable liver-fat-depositing effect of the extract.

Fig. 16. Oil-immersion photomicrograph of a section, stained by haematoxylin and eosin, of the parathyroid gland of a dog which received 4 daily injections of the extract. A mitotic figure may be seen in the centre of the picture. This picture illustrates the parathyrotropic effect of the extract.

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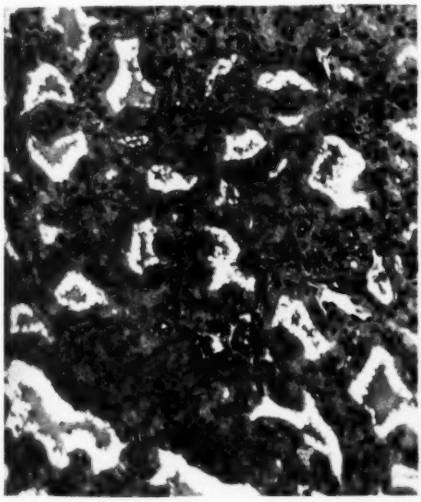

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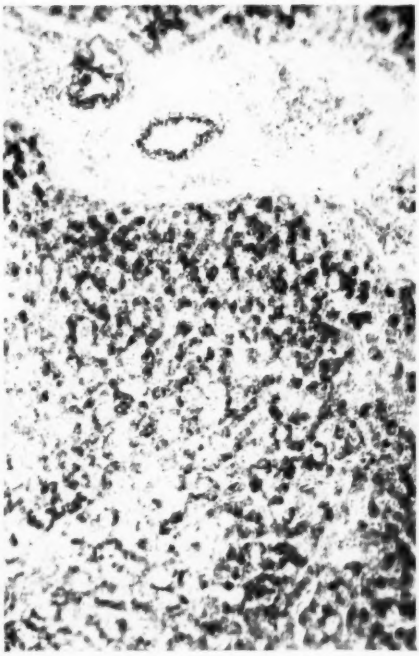

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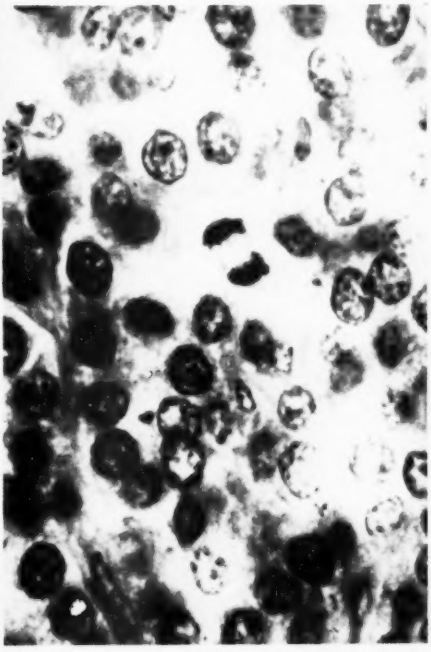

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PLATE 127

FIG. 17. Medium power photomicrograph of a section of the adrenal cortex from a control dog. The characteristic zona glomerulosa appears under the capsule at the top of the picture.

FIG. 18. Photomicrograph of widened zona glomerulosa and cellular hypertrophy observed when a dog is given 4 daily injections of extract. Magnification is the same as for Figure 17.

FIG. 19. Oil-immersion photomicrograph of zona glomerulosa of a dog given 4 daily injections of extract. Two mitotic figures as well as extensive cell vacuolation and cell hypertrophy are obvious. This, and Figure 18, illustrate the adrenocorticotropic effect of the extract.

FIG. 20. Low power photomicrograph of a section stained by haematoxylin and eosin of liver obtained from an animal which received 3 daily injections of the extract. The liver cells near the central vein are extremely well filled with glycogen, causing the vacuolation observed.

FIG. 21. Very low power photomicrograph of liver of an animal which received 7 daily injections of the extract. The liver cells of the greater part of each lobule are distended with clear fluid which contains glycogen.

FIG. 22. High power photomicrograph of an area selected from the section shown in Figure 21. There is little granular cytoplasm in these cells; the nuclei are frequently pyknotic and at one side of the cell. Glycogen stains showed that the cells contained considerable glycogen.

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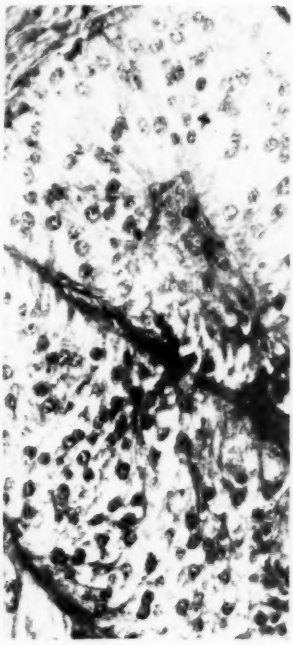

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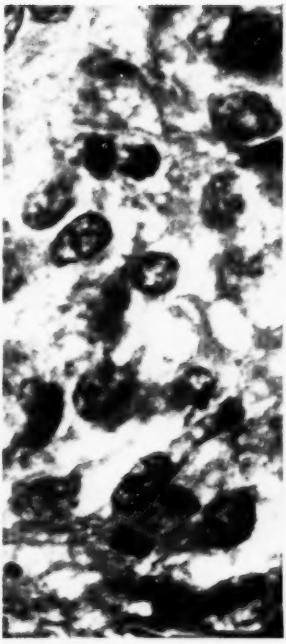

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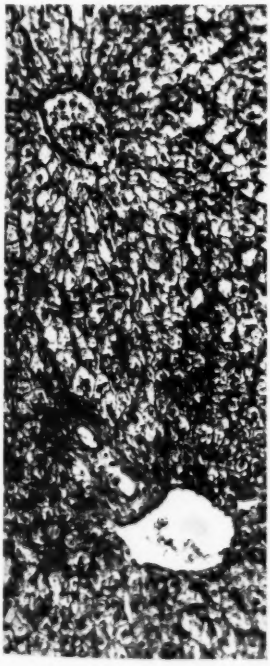

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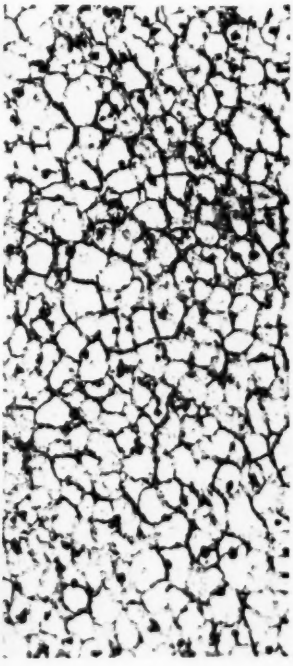

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PLATE 128

FIG. 23. Oil-immersion photomicrograph of a section stained by the Bowie method, of pancreas obtained from a dog 2 days after the last of 7 daily injections. One alpha cell can be seen to the left of the centre of the islet. The beta cells do not contain their normal granulation, the cytoplasm of these cells consisting only of the pale background in which the specific granules can usually be seen.

FIG. 24. Oil-immersion photomicrograph of a Bowie preparation of a pancreas obtained from a dog 3 days after the last of 7 daily injections. Three alpha cells with their large dark-staining granules can be seen on the left side of the islet. The beta cells which comprise the remainder of the islet show a returning granulation which is as yet not complete.

FIG. 25. Oil-immersion photomicrograph of an islet in a Bowie preparation of a pancreas obtained 4 days after the last of 7 daily injections of the extract. Beta cell granulation is approximately normal.

FIG. 26. Oil-immersion photomicrograph of a Mallory-azan preparation of an islet from an animal in permanent diabetes. Almost all the cells in the islet contained red granules and are alpha cells. In the photograph their cytoplasm is light. The reticulum in and about this islet is increased over normal.

FIG. 27. Oil-immersion photomicrograph of a Bowie preparation from the pancreas of a permanently diabetic dog. The cells of this islet can be identified as alpha cells by their large dark-staining granules.

FIG. 28. High power photomicrograph of an area of fibrosis bearing a superficial resemblance to an islet seen in a section stained by haematoxylin and eosin of the pancreas of one of the permanently diabetic dogs. This was the closest approach to an islet that was found in this pancreas.

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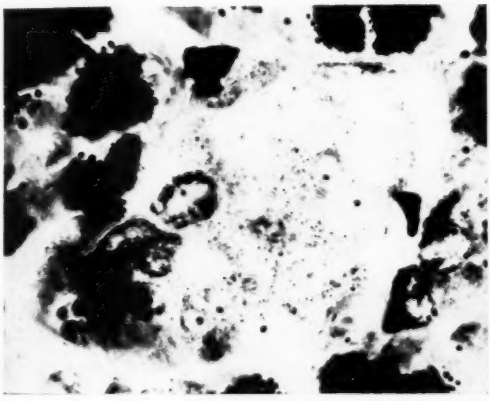

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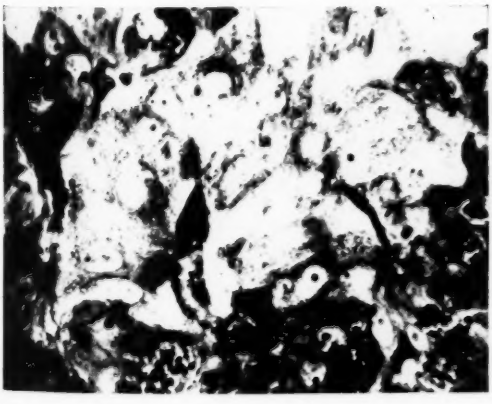

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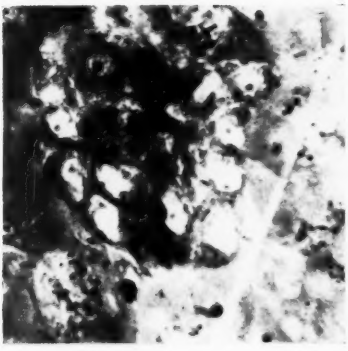

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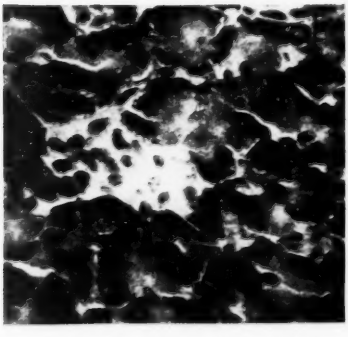

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Histopathogenesis of Diabetes

THE HISTOGENESIS OF GLIOMA RETINAE *

Report of Early Case with Review of Literature

K. Y. Ch'in, M.D.

(From the Department of Pathology, Peiping Union Medical College, Peking, China)

Glioma of the retina (retinoblastoma) is a rapidly progressing disease. At the time when the patient consents to operative removal, the condition is already anatomically far advanced and the histogenesis of the neoplasm cannot be determined. Operative and necropsy material rarely offers an opportunity for the study of the derivation of the tumor and in the literature there are recorded relatively few cases of early tumor whose point of origin from the retina can be definitely traced. For this reason the following case is reported.

Report of Case

Clinical History

A Chinese female infant, 21 months of age, was admitted with a rapidly progressive bulging of the right eye, present 20 days prior to admission. At the age of 1 month, a yellowish white, round spot was seen in the center of the right pupil, which persisted without any change in size. At the age of 11 months redness of the bulbar conjunctiva and redness and swelling of the eyelids on the right side were noticed but gradually subsided. Twenty days before admission redness recurred in the right eye, soon followed by protrusion of the eyeball and then of the right temporal region. The bulging increased steadily and the patient began to complain of pain in the temporal region 10 days before entry. The white spot in the cornea became ulcerated and there was some bleeding from it in the last 5 days.

Examination showed marked enlargement of the right eyeball with pronounced exophthalmos and lagophthalmos. The conjunctiva was congested and swollen and the cornea was totally destroyed and represented by a small, dry, dark stump. The eyeball was hard and fixed. A hard, protruding mass was present over the right temporal region lying deeply and apparently connected with the bone. The left eyeball was normal externally. Examination of the left fundus showed several well circumscribed, whitish masses. These masses were followed by repeated ophthalmoscopic examinations and were found to be stationary in size. Needle biopsy of the right temporal mass showed a round-celled malignant tumor, a questionable neuro-epithelioma.

* Received for publication December 30, 1940.

After admission, two exposures of deep X-ray therapy were given to the right eye and temporal region. The tumor became, however, steadily larger, with much bleeding from the right eyeball. Five weeks later, a tumor mass was noticed over the left lower jaw as well as extension of orbital growth into the oral cavity with ulceration of the buccal mucosa. The skull also showed signs of involvement by the tumor. The patient became drowsy and died in a very cachectic state 8 weeks after admission.

Postmortem Examination

The tumor of the right eye was far advanced. It had destroyed the entire eyeball except for the sclerotic coat, which was only partly preserved. The tumor had perforated this coat and spread widely by direct extension. On the right side, a huge tumor mass was found in the temporal region, and the orbital wall of the frontal bone, the great wing of the sphenoid and the anterior portion of the temporal bone were destroyed by it. Subperiosteal extension to the parietal and occipital bones was found. The tumor had spread medially and destroyed the ethmoid bone and filled the ethmoid sinuses. It had also spread upward, invading the cranial cavity and pushing the dura upward, and had spread to the opposite side to form a large mass in the left temporal region with subperiosteal extension to the left petrous and parietal bones. The brain showed marked compression and pressure atrophy of the right frontal, temporal and parietal regions. The tumor mass in the temporal region on both sides spread downward so as to destroy both maxillae (eroding the hard palate) and both sides of the mandible (filling the alveolar sockets). The tumor also had spread to the soft tissues of the right cheek and neck. Metastases were found in right eighth, ninth and tenth and left seventh and ninth ribs, femora, tibiae, fibulae, humeri, liver, pancreas and muscle of the right thigh.

The interesting finding in this case concerned the opposite (left) eye. The retina showed three well circumscribed, whitish nodules, circular and somewhat flattened in shape. They measured 4, 5 and 6 mm. in diameter, respectively, and were elevated above the inner retinal surface for 1 to 2 mm. One of them was situated immediately behind the ora serrata and the other two in the posterior segment of the retina behind the equator. The retina could easily be lifted away from the chorioid because these nodules had not invaded the latter coat. When both sides

of the retina were examined, the nodules were found to present a smooth surface on both sides and appeared to be confined within the limiting membranes of the retina. They bulged to a greater degree on the inner surface.

The smallest nodule was examined microscopically. It was found to be confined within the limiting membranes of the retina which were still intact. All of the retinal layers were normal up to the very margin of the nodule. At this point, the inner nuclear (granular) layer thickened and passed imperceptibly into the nodule. The cells of the nodule were small and round and had vesicular nuclei with fine chromatin granules and scanty cytoplasm and were identical in appearance with the cells of the inner nuclear (granular) layer except (1) that the former were hypertrophic with larger nucleus and a small amount of visible acidophilic cytoplasm (which was absent in the latter) and showed marked variation in the size of the cells, and (2) that the cells in the interior of the nodule were arranged in pseudo-rosettes. No true rosettes lined by columnar cells were present.

The nodule bulged more on the inner surface of the retina and therefore pressed upon or permeated into the inner layers of the retina much more than the outer layers. Thus the layer of nerve fibers, the ganglion cell layer (layer of nerve cells) and the inner reticular (molecular) layer were continued only for a short distance over the periphery of the nodule, while over the convexity of the nodule they were entirely destroyed and replaced by the cells of the nodule which was, however, throughout covered by the still intact inner limiting membrane. On the outer surface, where the nodule bulged only slightly, the outer reticular (molecular) layer was continued for some distance over the periphery of the nodule and then became lost over its convexity, while the outer nuclear (granular) layer, the outer limiting membrane and the layer of rods and cones were pushed outward with the outer nuclear layer moderately compressed and thinned out but were still intact throughout except at one spot where these layers had been destroyed and replaced by the tumor (nodule) cells which lined the free surface.

Another interesting finding was that at a distance of 5 mm. from this nodule, the inner nuclear layer showed another nodular thickening or hyperplasia, which was so small that it could be

recognized only microscopically. The histological picture of this nodule differed from that of the grossly visible nodule only in that hypertrophy of the individual cells and pseudorosette arrangement were not appreciable.

Discussion

Gliomas of the retina arise mainly from the ciliary portion (pars ciliaris retinae) and the posterior segment of the retina (Ewing [1]). According to Wintersteiner,[2] the origin is often multiple and chiefly from the posterior pole, while Eisenlohr [3] stated that the ciliary portion is the site of predilection and that the frequency of origin from it as compared to origin from the posterior segment is 11 to 7.

Grossly, multiple early gliomata have been described ophthalmologically by Hirschberg and Happe [4] and Hirschberg [5] as giving the appearance of acute miliary tuberculosis of a serous membrane. Multiple focal opacities, semiglobular elevations and small nodules have also been noted. Microscopically, glioma retinae may arise from the inner layers of the retina and invade and be situated mainly in the vitreous humor, known as glioma endophytum; or it may arise from the outer retinal layers and be situated mainly between the retina and the chorioid, known as glioma exophytum. Hirschberg and Happe [4] described an early tumor arising as circumscribed collections of round cells in the inner nuclear layer, which they considered to be the common origin for this tumor. Flexner [6] described a fair-sized tumor which, although connected with the retina throughout a considerable part of its extent, was seen to originate at a point of microscopic size situated in the external nuclear layer. Schweigger [7] observed also a tumor arising as a localized hyperplasia of the cells of this layer. Eisenlohr [3] stated that the tumor at times arises from the inner, and at times from the external nuclear layer. Iwanoff's [8] early tumor was in the form of an interstitial infiltration of the nerve fiber layer by small round cells even without causing thickening of that layer. Leber [9] stated that the fibrillar (reticular) layers of the retina can also be the starting point of gliomas. Delafield [10] described a tumor mainly involving the nerve fiber layer and inner nuclear layer and thought that it could arise anywhere inside the outer reticular layer. Knapp [11]

found the inner granular (nuclear) layer to be the starting point of the bulk of a tumor but at the same time observed multiple foci of neoplastic proliferation in the outer nuclear layer and in the inner (reticular, ganglionic and nerve fiber) layers of the retina. The retina was two or three times its normal thickness and the normal elements were destroyed and replaced by tumor cells but both limiting membranes were intact and only pushed aside. Thus Iwanoff,[8] Jackson [12] and Stout [13] have concluded that the tumor can arise from any or all of the layers of the retina.

Jokl [14] described an early tumor situated in the center of the optic nerve head and found the tumor cells to be identical in appearance, and also continuous, with the cells of a tonguelike process of glial tissue around the hyaloid artery. Since Seefelder [15] had described a migration of glial cells from the optic papilla in a fetus of 7 months' intra-uterine life to form a tumor-like mass of glial tissue around the hyaloid artery and his own observation had shown a direct continuity between the tumor and glial tissue around the artery, Jokl considered such glial tissue the origin of the neoplasm and viewed the tumor in the light of a congenital malformation. He further supported his view by referring to the coexistence of this tumor with such malformations as microphthalmos, coloboma and pupillary membrane as reported in the literature. The fetal or congenital origin of glioma retinae has also been emphasized by Eisenlohr.[3]

The case herein reported is one of bilateral glioma retinae, in which the tumor on one side was far advanced with widespread local extension and distant metastases while the tumor on the other side was at a very early stage, still confined within the retina and with a clearly demonstrable origin from the inner nuclear layer. With a large tumor in the right eye, it is theoretically possible that the small nodules in the left eye were metastatic, but in favor of their primary origin are the following findings: (1) the gradual thickening of the inner nuclear layer and its gradual passage into the nodule without a perceptible margin of transition (Figs. 3 and 4); (2) the microscopic nodular swelling of the inner nuclear layer elsewhere (Fig. 5); (3) that the nodule of the left eye showed a histological picture different from that of either the primary tumor of the right eye or its

metastases. In the latter, the distinct pseudorosette arrangement of the tumor cells was absent, and the tumor cells were much larger, much more hyperchromatic and much more irregular in shape. This disease is bilateral, according to Ewing [1] in 23 per cent, and according to Knapp [16] in 20 per cent, of those affected. The tumor is less advanced in the second eye, or may appear after an interval of 3, 4, or even 13 years (Knapp [16]) following the enucleation of the tumorous eye as new primary growth. In my case, the age (21 months) of the patient, the location of the early gliomata (in the posterior segment) and their multiplicity, the origin from the inner nuclear layer and the histological picture of a nodular hyperplasia of the cells of the nuclear layer are all typical for this disease, as a review of the literature has shown. The stationary size of the three nodules as found by repeated fundal examination bears out Ewing's statement that the initial growth of the tumor may be very slow.

It may be pointed out that in the early lesions of the retina herein described there is a certain amount of overlapping between "malformation" and "neoplasm." If the microscopic nodular swelling of the inner nuclear layer remains quiescent, it may justifiably be called malformation of the retina. This situation reminds one of another lesion of the nervous system, namely, tuberous sclerosis, which may remain quiescent as a malformation but may develop into a malignant neoplasm (glioblastoma multiforme).

Summary

An early glioma retinae (retinoblastoma) with clearly demonstrable origin from the inner nuclear layer and still confined within the limiting membranes of the retina is described and the literature on early glioma retinae is reviewed with reference to the site of origin and histogenesis.

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DESCRIPTION OF PLATES

PLATE 129

FIG. 1. Horizontal section through the head and eyes, slightly below the level of the pupils. The right eye has been entirely replaced by dark tumor tissue but the sclerotic coat is still preserved. A large tumor mass in the right temporal region has partly destroyed and partly surrounded the right frontal bone, and has extended posteriorly and subperiosteally to the right temporal bone, and medially to destroy the posterior portion of the ethmoid bone. The tumor mass seen in the left temporal region was continuous with the right temporal mass at a higher level. The left eye showed one whitish nodule on the posterior segment of the retina and another seen in profile as a whitish band just behind the ora serrata. 7/10 natural size.

FIG. 2. Drawing of the sectioned left eye, showing the two whitish nodules of the retina, one just behind the ora serrata and the other in the posterior segment, viewed from a slightly different angle. The third nodule referred to in the text was on the opposite half of the eyeball and therefore could not be shown in this picture. Natural size.

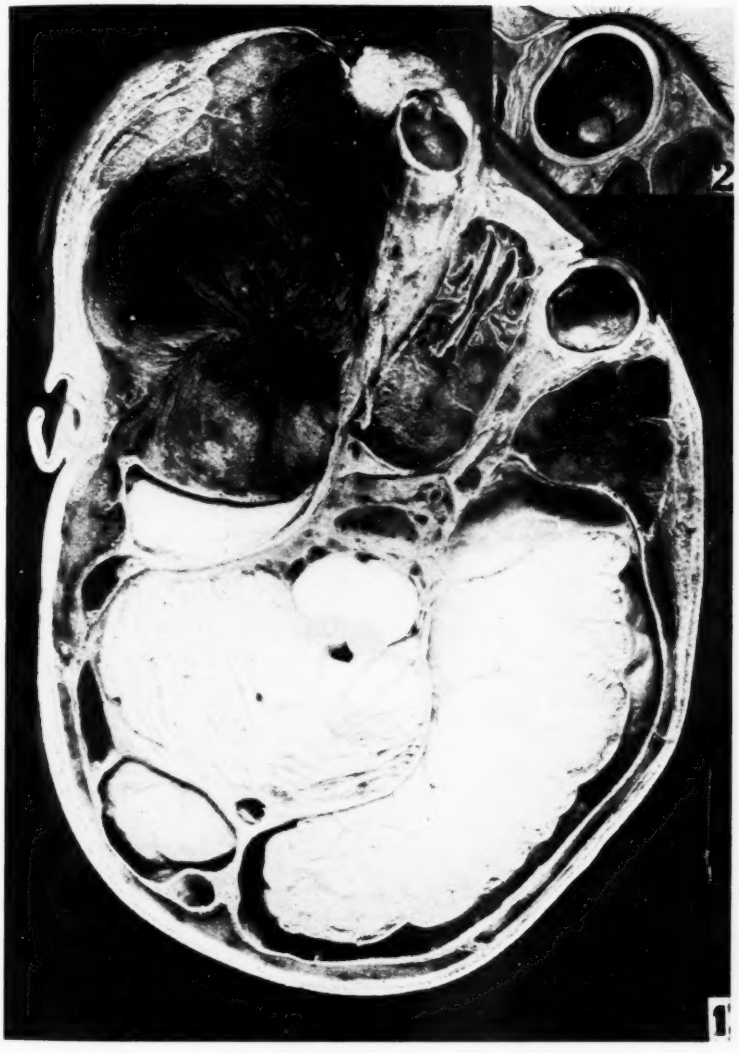
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Plate 130

Fig. 3. Low power view of the smallest nodule of the left retina. At the right and left margins of the picture, the normal retinal layers are intact, while in the central portion the inner nuclear layer widens into a tumor nodule. The nodule bulges more on the inner surface (below) of the retina, where it is, however, still completely enveloped by the inner limiting membrane. On the outer surface (above), the outer nuclear layer can be seen to cover the nodule completely except at one area midway between the left margin and the middle line of the nodule. The deeper retinal layers are continued, on both the inner and outer surfaces, for only a short distance over the periphery of the nodule. × 20.

Fig. 4. Peripheral portion of the nodule with the adjacent normal retina. From above downward can be seen the layer of rods and cones (gray in color, arranged as a palisade and somewhat torn by artefact), the outer limiting layer (a gray, somewhat wavy membrane), the outer nuclear (granular) layer (very broad and consisting of dark nuclei), the outer reticular (molecular) layer (pale), the inner nuclear (granular) layer (much narrower than the outer nuclear layer), the inner reticular (molecular) layer (much broader than the outer reticular layer), the layer of ganglion (nerve) cells (very thin, only two or three cells thick), the layer of nerve fibers (pale and broad) and the inner limiting membrane (as a sharp line). The cells of the nodule can be seen to arise clearly from the inner nuclear layer which gradually increases in thickness and passes imperceptibly into the nodule. The various retinal layers are seen to continue over the peripheral portion of the nodule. × 155.

Fig. 5. Portion of retina, 5 mm. away from the nodule illustrated in Figure 3, showing a microscopic nodular swelling of the inner nuclear layer. × 155.

Fig. 6. Central portion of the nodule illustrated in Figure 3, and its outer surface, showing the arrangement of the tumor cells in pseudorosettes. At the right margin of the figure can be seen the rods and cones, the outer limiting membrane and the persisting outer nuclear layer. × 220.

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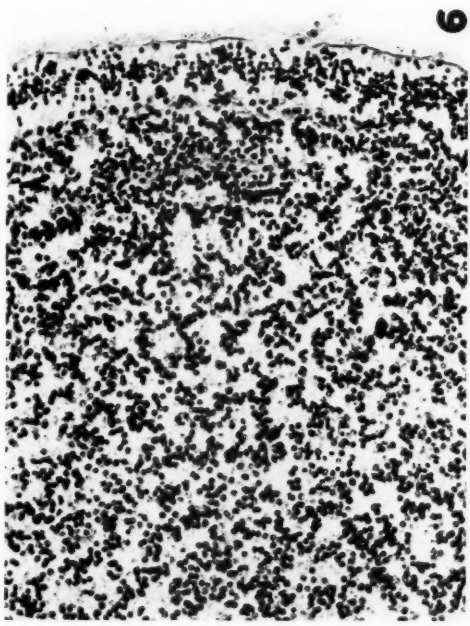

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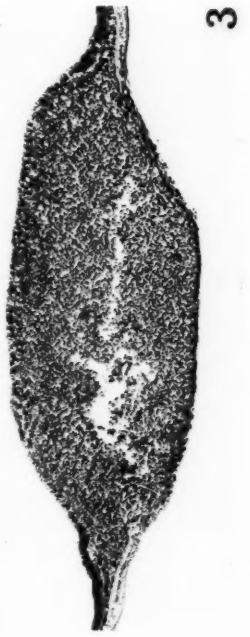

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CARCINOMA OF CERUMINOUS GLAND *

SHIELDS WARREN, M.D., and OLIVE GATES, M.D.
(From the Laboratory of Pathology, Collis P. Huntington Memorial Hospital, Boston, Mass.)

We report one case of carcinoma of ceruminous gland. Judging from our own experience and from the literature this is one of the least common tumors.

REPORT OF CASE

A male, 78 years old, over a period of 1 year, developed a subcutaneous tumor in the hollow behind the right ear which was bounded by the lobule, lower auricle and mastoid process and increased more rapidly in the latter part of the year. Right lower facial paralysis developed 6 months after the tumor was noticed. Latterly the slightly elevated eminence formed by the tumor became ulcerated. The tumor was excised by Dr. C. C. Lund by wide dissection, including the posterior tip of the parotid and the deeper muscles and extending to the skin of the inferior aspect of the external auditory meatus. A complete right facial paralysis followed the operation.

Gross Description

The specimen consisted of an oval mass of tissue with skin on one surface, measuring 4 by 2.5 cm., with underlying tissue 2 cm. in thickness. The skin surface was smooth and not remarkable except for a sharply outlined ulcer, 1.2 cm. in diameter, in the center. Yellowish brown, granular tissue was present in the ulcer. The specimen as a whole was extremely firm. The cut surface showed juicy, resilient tissue at the ulcer and for about 1 cm. under the surrounding normal skin. One cm. from the skin surface the superficial tumor merged with a scirrhous, irregularly outlined mass 2 cm. in diameter. Cysts containing slightly yellowish, granular fluid, varying from 0.2 to 0.6 cm., were present in this more dense tissue. The facial nerve emerged from the edge of this mass. At one end of the specimen a small portion of salivary gland was recognized.

Microscopic Examination

Microscopic sections showed an adenocarcinoma varying markedly in degree of differentiation, the most anaplastic portions being at the ulcerated surface of the skin. Here the tumor had

* Received for publication April 11, 1941.

no uniform architecture, but grew in irregular strands and clumps with little intervening corium. There was no connection with the overlying skin. The cells were large and polyhedral with a finely granular or foamy cytoplasm which tended to be neutrophilic. In size the nuclei were moderate to large. Mitotic figures, some of which were atypical, were not as numerous as one might expect from the degree of anaplasia. At one point the tumor had extended slightly into a lobule of parotid gland. But in the scirrhous part of the tumor the cell structure became more differentiated and a distinct architectural pattern was obvious. The cells were smaller and arranged in alveoli, some of which were distended with secretion and débris to form minute cysts. In one part of the tumor near the under surface of the specimen, and at the opposite end from the parotid, the structure was so well differentiated that in a given field it was impossible to be sure whether the alveoli were an adult form of the tumor or were glands surrounded by tumor, so closely did they resemble the normal ceruminous gland. These alveoli, each about twice the size of an alveolus of a sweat gland, were formed of tall cuboidal to columnar cells having the characteristic lipped margins of the ceruminous and apocrine glands and a rather small nucleus placed in the center of the cell or slightly toward the basement membrane. One or two spindle-shaped nuclei, which might be either in smooth muscle cells or in fibrocytes, partly encircled the glands. The typical myo-epithelial cells of the sweat glands and also occasionally of the ceruminous gland were not seen.

The most interesting feature of the tumor cells in the deep scirrhous portion, allying them to the superficial anaplastic tumor, was the reticulated, foamy and finely granular cytoplasm. Fine fat droplets could be stained with Sudan IV. In a majority of the cells, the granules had the same neutrophilic tint as the cytoplasm as a whole, but in many the granules were much larger, stained a deep blue and were clumped at the free end of the cell or around the nucleus. In about one-fourth of the glands there were amber granules in the cytoplasm. Many of the granules gave a positive iron reaction. The epithelium lining the cystic alveoli was less uniform; in some places it was flattened, in others many-layered and in still others there were miniature papillary cystadenomas. Cellular débris, blood and amber extracellular pigment granules

were present in many of the cysts. It seemed rather curious that those well formed glands were lying in perivascular lymphatics and penetrating nerve trunks whereas the less differentiated tumor was not seen in either lymphatics or blood vessels. There was no evidence of gross metastasis.

Discussion

The differential diagnosis lies between carcinoma of an apocrine gland and carcinoma of a ceruminous gland. Both are modified coil or sweat glands. Their normal histology is similar. The chief points of difference are in the rather more conspicuous pigment and lipoid in the ceruminous gland, which at best is a rough quantitative distinction, and the more conspicuous smooth muscle which sometimes surrounds the ceruminous glands.

These histologic variants are of no practical interest in this case for the following reasons:

(1) Judging from the degree of differentiation of the various parts of the tumor with which we are concerned, it originated in the deep portion of the specimen near the auditory canal.

(2) Apocrine glands rarely, if ever, occur in this region.

(3) Only the apocrine glands of the axilla or genital region contain readily demonstrable lipoid or pigment.

From the paucity of reports of tumors of the ceruminous gland in the literature it is fair to assume that this is an extraordinarily rare tumor. Montpellier and Laffargue [1] in 1938 published a careful and convincing report of carcinoma of the ceruminous gland with very good illustrations. As in our tumor, there were very undifferentiated portions. The authors had seen a similar tumor in the ear of a cat. Adenomas of the ceruminous gland, reported by Brock [2] and by Sprenger and Prietzel,[3] also appear correctly classified. In all of these cases the tumor appeared to originate from the intimately associated normal ceruminous gland.

Sprague [4] in 1898 and Yearsley and Butterfield [5] in 1924 reported a case with appearances suggestive of origin in the ceruminous gland. Only the probability of carcinoma of ceruminous gland was claimed by these authors. Sprague's tumor was highly invasive, infiltrating the skull and dura. Yearsley and Butterfield's case was apparently of a low degree of malignancy.

The 3 positive and 2 probable cases of tumors of the ceruminous gland differ from ours in that they all presented in the external auditory canal, and all but 1 from the superior surface of the canal.

Tumors of glandular origin of the ear have been a subject of much interest because of their extreme rarity. Nearly all of them originate in the middle ear. Klingel [6] in 1891 reported an adenoma of a sebaceous gland of the ear canal. Parrish [7] in 1924 reported a highly malignant tumor of the external auditory meatus which eroded deeply into the skull and caused death. This was diagnosed as a squamous cell adenocarcinoma.

Newhart [8] reviewed the literature from 1899 to 1917 and found 34 cases of carcinoma of the middle ear. One case of adenocarcinoma of the middle ear was found by Furstenberg [9] among 40,000 admissions. Fraser [10] found 15 cases of carcinoma of the external auditory meatus and middle ear among 6,605 "affections" of the ear, including 2 cases of "malignant sebaceous adenoma" from the external auditory meatus. Three cases of malignant tumor of the middle ear, among 35,000 cases seen from 1919 to 1931, were reported by Richter.[11]

Robinson [12] reported that in a group of 212,000 clinic patients there were 19 cases of carcinoma of the external auditory canal and 5 arising from the middle ear. Alonso [13] reported 24 cases of malignant tumor of the auricle, 5 of the mastoid region, 5 of the external auditory canal and 6 of the ear drum and middle ear.

In 1935 Schall [14] reviewed the tumors at the Massachusetts Eye and Ear Infirmary and found no case of adenocarcinoma among some 90,040 pathological specimens from the ear. In his personal practice he had 1 case of adenocarcinoma involving the external auditory meatus and middle ear among 4 cases of carcinoma in this location. Thorell [15] reported from the Radiumhemmet that there was no case of adenocarcinoma among 13 cases of malignancy of the middle ear. Lukens [16] in 1936 reported 1 case of adenocarcinoma of the external auditory canal with some mucoid secretion which he considered of low malignancy only. He accepted only 4 previously reported cases of carcinoma of the external auditory canal: Fraser's 2 cases, Schall's case and Furstenberg's case.

It appears that carcinoma of the external auditory canal is

uncommon and adenocarcinoma extremely rare. Adenomas and carcinomas of the sebaceous glands of this region are reported occasionally, but a tumor having origin in a ceruminous gland is a curiosity.

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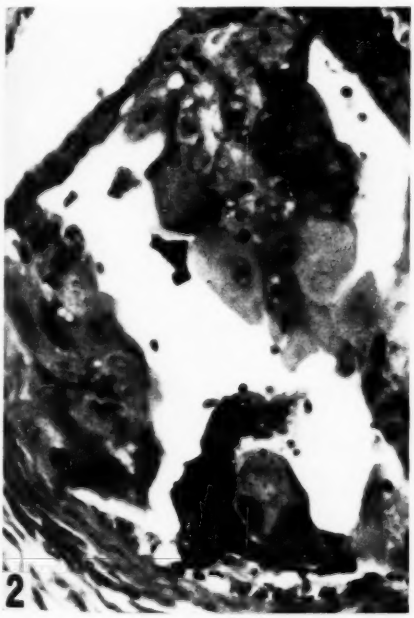
DESCRIPTION OF PLATES

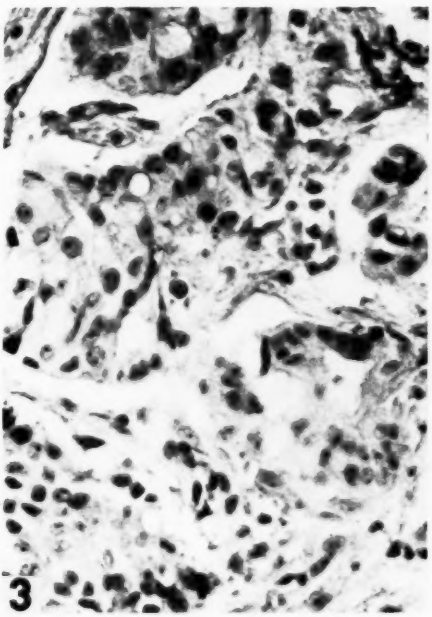
PLATE 131

FIG. 1. Section through specimen removed, showing skin at upper border and extent of tumor.

FIG. 2. Portion of tumor showing variation in size and character of epithelium. × 360.

FIG. 3. Portion of tumor showing epithelial masses and some vacuolated cells. × 360.





Warren and Gates

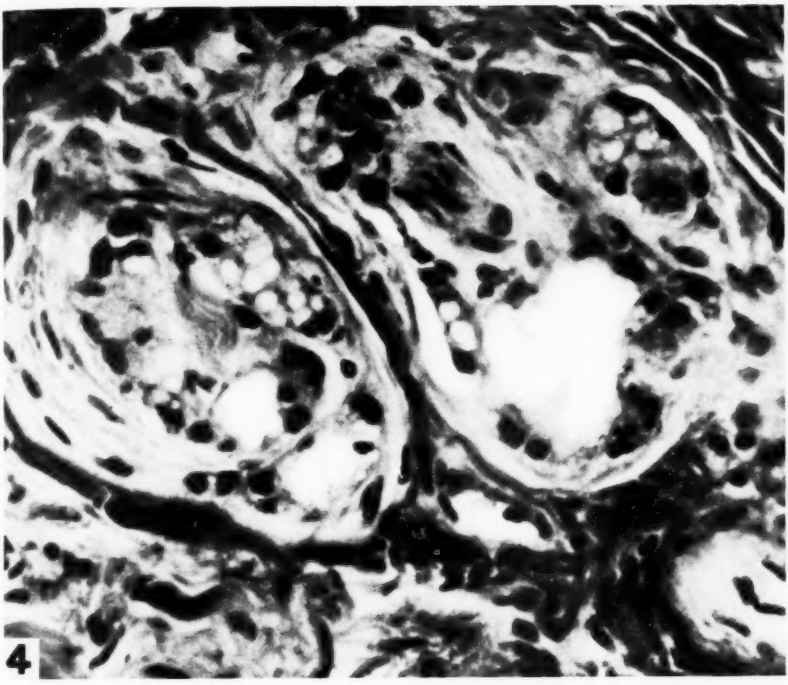
Carcinoma of Ceruminous Gland

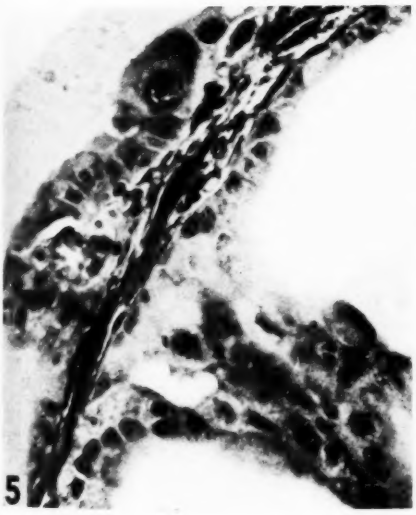
PLATE 132

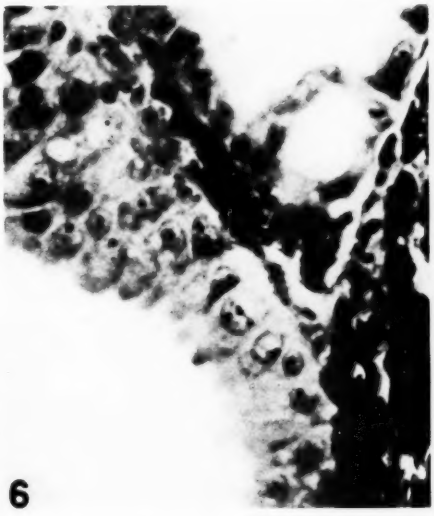
FIG. 4. Invasion of nerve by carcinoma of ceruminous gland. × 500.

FIG. 5. Portion of tumor showing a neoplastic giant cell. × 320.

FIG. 6. Portion of tumor showing lipping of tumor cells. × 510.







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Carcinoma of Ceruminous Gland

UNIV. OF MICH.

MULTIPLE SKIN TUMORS IN MICE FOLLOWING A SINGLE PAINTING WITH 9:10 DIMETHYL–1:2 BENZANTHRACENE *

L. W. Law, Ph.D.†

(From the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine)

The chief problem with which most investigators of experimental "tar" cancer have been concerned is whether carcinogenic agents induce cancer because of their constitutional effects or whether the reaction produced is merely a local manifestation. This is particularly difficult to determine. As Seelig and Cooper [1] pointed out, most reasoning has been indirect and as yet there is no satisfactory solution of the problem.

During the course of an experiment testing the susceptibility of different inbred lines of mice to painting with the carcinogen 9:10 dimethyl–1:2 benzanthracene,‡ some interesting data were obtained concerning the reaction of the C57 brown strain of mice. Previously, Mider and Morton [2] had shown this strain to be especially sensitive to paintings with methylcholanthrene.

The C57 brown strain of mice has been maintained at this laboratory for more than 40 generations of brother-sister matings. Epithelial tumors are rare. Mammary tumors appear in approximately 5 per cent of the breeding females while spontaneous papillomata and carcinomata, other than mammary, have but rarely been observed.

Thirty mice 4 weeks of age were painted twice a week middorsally from the occiput to the near lumbar region with a 0.3 per cent solution of 9:10 dimethyl–1:2 benzanthracene in thiophene-free benzene. This was applied with a No. 6 camel's hair brush. Paintings were continued for 12 weeks. More than half of these mice developed multiple persisting papillomata or carcinomata. All but two of these growths appeared within the painted area. The majority of mice surviving the toxic effect of the carcinogen developed a leukemoid condition involving only the liver and spleen.

Ten mice were given a single application of the carcinogen in the same region. After the solution had completely evaporated,

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† Finney-Howell Foundation Fellow.

‡ Supplied through the courtesy of W. E. Bachmann, University of Michigan.

these mice were placed 2 or 3 in a cage and given the same food—purina fox chow—as the first group. Epilation occurred within 1 week, followed by a growth of white hair in the epilated region. There was no ulceration of the skin.

A papilloma appeared on the right foreleg of ♂ B1, 169 days after painting. This was found to be carcinomatous at approximately 238 days. The second growth appeared on the right foreleg of ♂ B23, 199 days following painting. This proved to be carcinomatous at 224 days. Following these there appeared in all, twenty-five papillomata on the 10 mice given single paintings (Table I). There were eight growths on ♂ B1: four of these be-

TABLE I

Multiple Skin Tumors Following a Single Painting with 9:10 Dimethyl-1:2 Benzanthracene

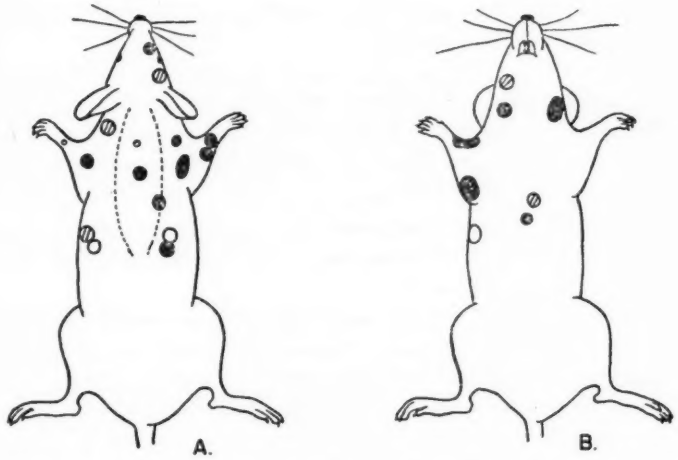
Mouse No.	Papillomata		Carcinomata		Position
	No.	Appearance (days)	No.	Appearance (days)	
♂B1	8	169	4	238	Dorsal—OPA*
		249		280	Dorsal—OPA
		339; regressed			Dorsal—OPA
		314; regressed			Within painted area
		279		339	Within painted area
		274; persisted			Dorsal—OPA
		327; regressed			Ventral
		281		329	Ventral
♂B2	4	224	2	254	Dorsal—OPA
		240; persisted			Dorsal—OPA
		254		299	Within painted area
		314; persisted			Dorsal—OPA
♂B3	2	270	2	300	Dorsal—OPA
		240		272	Dorsal—OPA
♀B8	1	377	1	421	Ventral
♀B9	3	279	1	319	Ventral
		335; regressed			Ventral
		305; regressed			Dorsal—OPA
♂B22	2	240; persisted	0		Dorsal—OPA
		330; persisted			Ventral
♂B23	1	199	1	224	Dorsal—OPA
♂B24	2	240	1	347†	Ventral
		274; regressed			Dorsal—OPA
♀B29	1	304; regressed	0		Ventral
♀B30	1	283	1	328‡	Dorsal—OPA

* OPA = outside painted area.
† Transplanted subcutaneously to 8 C57 brown mice. Positive malignancy.
‡ Transplanted subcutaneously to 7 C57 brown mice. Positive malignancy.

came carcinomata, three regressed, while one persisted until necropsy as a papilloma.

Thirteen of the papillomata became transformed into carcinomata, seven regressed completely and five persisted as such without much apparent change. Malignancy was detected by a decided change in the rate of growth at the base of the lesion, followed usually by ulceration. In some cases diagnosis was confirmed by biopsy. Histological study was made of all lesions.

Twenty-two of the tumors appeared outside of the painted area (Text-Fig. 1). These were confined mostly to the forelegs and head region. Eight growths appeared on the near-ventral or ventral region. It is interesting to note that none of the tumors



TEXT-FIGURE 1. Distribution of skin tumors in C_{57} brown mice given a single application of 0.3 per cent 9:10 dimethyl-1:2 benzanthracene in benzene. A, dorsal; B, ventral. Solid areas indicate carcinomata, hatched areas indicate papillomata persisting as such, unmarked areas indicate papillomata which regressed. Dorsal painted region shown by dotted lines.

appeared behind the base of the painted area (lumbar region), whereas numerous growths appeared in front of the tip of the painted area (occiput region).

Two of the malignant growths were transplanted to 1-month-old mice of the C57 brown strain. Both proved to be slowly growing carcinomata which invaded muscle. One of these growths

in ♂ B23 had much the appearance of adenocarcinoma of a mammary gland.

In 1934, Reinhard and Thibaudeau [3] called attention to a peculiar and unusual development of multiple tumors of the skin in an inbred strain of mice painted with tar for a period of from 8 to 12 weeks. The tumors appeared both dorsally and ventrally. These growths, mostly sebaceous adenomata in the final stage, were not characteristic, however, of ordinary tar tumors. In a later report, Reinhard and Candee [4] suggested that ingestion of the tar material from the backs of mice or from the cages may account for this unusual phenomenon. This seems a very remote possibility in our experiment since the mice were given only one application. Furthermore, the growths produced were identical with those resulting from continuous paintings and were restricted to the anterior part of the body.

It has been found by the British group [5] that epitheliomata produced by multiple paintings with a 0.06 per cent solution of the 5:9:10 trimethyl–1:2 benzanthracene compound appeared at the edge of the painted area and not at its center, suggesting that the optimal conditions for tumor production are in the regions of considerable dilution. Again, such an explanation would fail to account for those growths appearing on the forelegs and on the near-ventral and ventral surfaces.

Since mice of this strain receiving multiple paintings of 9:10 dimethyl–1:2 benzanthracene developed lesions almost entirely within the painted area, it seems very unlikely that scratching or accidental brushing would account for the unusual distribution of growths in singly painted mice. In fact, the position of some of the abnormal growths is such that scratching could not account for their appearance.

Certain definite conclusions can be drawn. A very small amount of carcinogen is required to initiate abnormal growth of the epithelial cells in mice of the C57 brown strain. Once a benign growth is begun, no further external application of carcinogen is required to produce malignancy. The solution to the question of whether these induced tumors result from a general constitutional effect must await further experimentation.

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THE RELATIVE SUSCEPTIBILITY OF THE SYNAPTIC TERMINALS AND OF THE PERIKARYON TO ARREST OF THE CIRCULATION OF THE BRAIN *

HERMAN KABAT, Ph.D., and MELVIN SCHADEWALD, Ph.D.
(From the Departments of Physiology and Anatomy, University of Minnesota, Minneapolis, Minn.)

The opinion is widely held that the synapse is more sensitive to lack of oxygen than is the cell body of the neuron.[1,2] The evidence on which this hypothesis is based comes largely from anatomical studies of the vascularity of different portions of the nervous system.[3]

Recent studies do not support this view. Craigie [4] noted that some areas rich in synapses are poor in capillaries. Bronk [5] found that the synapse was not more sensitive to anoxia than the perikaryon in the stellate ganglion and Gerard [6] observed that the apparent metabolism was higher in the perikaryon than in neuropil in the brain.

An opportunity presented itself to study the relative resistance of different portions of the neuron to arrest of the circulation of the brain. Studies were made of the morphological changes produced in the perikarya of the Purkinje cells of the cerebellum and in their associated synaptic terminals by equal arrest of circulation in the two adjacent structures. This investigation indicates that the synaptic terminals have a greater resistance to damage by anoxia than have the perikarya with which they are associated.

METHODS

The blood flow through the brain was stopped completely for periods of 2 to 8 minutes in adult dogs. The method of producing complete temporary arrest of the cephalic circulation by means of a cervical pressure cuff has been described elsewhere.[7] Six animals were subjected to stasis in the brain and one served as a normal control. The brain was removed immediately after death and fixed

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in formaldehyde. Portions of the cerebellum were dehydrated in dioxane, embedded in paraffin, sectioned at 8 μ and stained with hematoxylin and eosin, thionin and in some cases with the Bodian silver technic and phosphotungstic acid-hematoxylin. Other blocks from the same cerebellum were stained according to the block silver method of Cajal, modification 4a. The material stained by the Cajal method was embedded in paraffin and sectioned at 10 μ.

Results

The Purkinje cells of the cerebellar cortex are among the structures in the brain of the dog most sensitive to arrest of the circulation. These cells show pathological alterations after only 2 minutes of stasis, while after 8 minutes of arrest of the circulation of the brain almost all of them disintegrate and disappear. On the other hand, the other neurons of the cerebellar cortex are resistant to arrest of the circulation, since they remain morphologically normal after the Purkinje cells have disappeared (Fig. 1). The granule cells of the cerebellar cortex are even more resistant to stasis than are many nuclei of the brain stem. Sensitivity of Purkinje cells and resistance of other neurons of the cerebellar cortex to arrest of circulation has also been demonstrated in the cat.[8] Physiological evidence also supports the view that the Purkinje cells are very sensitive to arrest of blood flow.[9,10]

All of the types of boutons terminaux described by many authors [11] can be seen on the surface of the normal Purkinje cell (Fig. 2). These types include: simple terminal loops, filamented terminal loops, fibrillated bulbs and boutons-en-passant. Similar structures have been demonstrated in the experimental material to be described. Pathological changes in the boutons terminaux were never observed.

The synaptic terminals on the Purkinje cells originate in neurons of the spinal cord, brain stem and cerebellar cortex. The perikarya of the neurons in the spinal cord were not subjected to arrest of blood flow. The neurons of the brain stem which send their fibers to the Purkinje cells showed no significant pathological alterations as a result of the periods of stasis employed in this investigation. The neurons of the cerebellar cortex other than the Purkinje cells were also resistant to these periods of arrest of circulation. While some synaptic terminals arise as collaterals of

the Purkinje axons themselves, these are relatively few in number. Therefore (with the latter terminals as a minor exception) pathological alterations in the boutons terminaux on the Purkinje cells could occur only as an effect of arrest of blood flow on these boutons themselves.

Dog No. 3, a normal adult male, subjected to arrest of the circulation of the brain for 4 minutes, was sacrificed at the end of 3 months. In thionin-stained sections, the Purkinje cells showed shrinkage and pyknosis in some instances, and vacuolization and chromatolysis in others. Many Purkinje cells had completely disappeared. Normal boutons terminaux were present about the perikarya of both the pyknotic and vacuolated cells in Bodian preparations.

Dog No. 13, a normal adult male, subjected to arrest of the circulation of the brain for 8 minutes, was sacrificed at the end of 2½ months. Hematoxylin and eosin, and thionin preparations showed that almost all of the Purkinje cells had disappeared (Fig. 1). In many folia, no Purkinje cells could be found. The few Purkinje cells remaining were obviously pathological. Material stained by the Bodian method revealed baskets of nerve fibers surrounding the absent Purkinje cells (Fig. 3) and within these baskets small-looped synaptic terminals of normal morphology were observed. Normal boutons terminaux were also demonstrable on the severely damaged Purkinje cells which were still present.

*Dog No. 18,** an adult female in the last week of pregnancy, was subjected to 2 minutes of arrest of the circulation of the brain and was sacrificed at the end of 2½ months. Examination of the thionin preparations revealed that while relatively few Purkinje cells had disappeared, almost all of the cells showed pathological changes such as chromatolysis, shrinkage and pyknosis, and vacuolization. Normal boutons terminaux were seen on the damaged Purkinje cells in preparations stained by the Cajal method. With the phosphotungstic acid-hematoxylin stain, marked proliferation of astrocytes around the pathological Purkinje cells was evident.

*Dog No. 6,** an actively lactating adult female subjected to

* Pregnancy, lactation and puberty rendered animals more susceptible to arrest of the brain circulation.[12]

arrest of the circulation of the brain for 4 minutes, remained in coma and survived for 6 days. Thionin-stained sections showed a moderate disappearance of Purkinje cells but the cells remaining all showed shrinkage, pyknosis, eccentricity of the nucleus with marked folding of the nuclear membrane, severe chromatolysis or vacuolization. In Cajal preparations, normal boutons terminaux were found in the tangled masses of axons which remained at the site of completely disintegrated Purkinje cells. Normal synaptic terminals were also observed on the pathological Purkinje cells.

*Dog No. 7,** a female in her first estrus subjected to 6 minutes of arrest of the circulation of the brain, remained in coma and survived for 9 days. Practically all of the Purkinje cells had disappeared from the cerebellar cortex. On pathological fragments of Purkinje cells which remained as well as in the baskets of fibers at the site of the absent Purkinje cells, morphologically normal boutons terminaux were found.

*Dog No. 24,** an adult female in early pregnancy subjected to arrest of the circulation of the brain for 7 minutes, remained in coma and survived for 11 days. The sections stained by Cajal's method revealed almost complete disappearance of the Purkinje cells. Normal boutons terminaux remained in the baskets of fibers surrounding the site of the completely disintegrated Purkinje cells (Fig. 4).

Discussion

The problem of the relative resistance to lack of oxygen of different portions of the nerve cell is a difficult one and no conclusive evidence is yet available. While the hypothesis that the synaptic ending is the portion of the neuron most susceptible to anoxia has been widely accepted, the evidence on which this hypothesis is based is meager and inconclusive. Wolff [3] stated that vascularity varies quantitatively with the number of synaptic structures and does not vary with differences in the number or mass of nerve-cell bodies. On the basis of studies of vascularity of various portions of the nervous system, he suggested a higher metabolic rate and greater sensitivity to anoxia at the synapses. Similar data on vas-

* Pregnancy, lactation and puberty rendered animals more susceptible to arrest of the brain circulation.[12]

cularity have been reported by Lorente de Nò [13] and Campbell.[14]

Data concerning the relative vascularity of different parts of the nervous system cannot serve as a sound basis for the determination of the relative metabolic rate and resistance to anoxia of different parts of the neuron. Areas rich in synapses are not always highly vascular.[4] Furthermore, the quantitative correlation between metabolic rate and resistance to anoxia on the one hand and vascularity on the other hand is generally poor.[6] A striking example of this lack of correlation is provided by the supra-optic nucleus in the hypothalamus. This nucleus, which has the greatest vascularity of all nerve centers in the brain,[15] is nevertheless among the most resistant to destruction by arrest of the circulation of the brain. In a dog in our series subjected to arrest of the circulation of the brain for 19 minutes and surviving for 9 days, the supra-optic nucleus appeared histologically normal despite disintegration and disappearance of the nerve cells of the cerebral cortex, Purkinje layer of the cerebellum, corpus striatum, thalamus and many nuclei of the brain stem as far caudally as the medulla.

A direct study by Bronk [5] of loss of function of the stellate ganglion as a result of anoxia revealed that the perikaryon was the first structure to lose its irritability. In this type of experiment, it was impossible to determine whether function was maintained in the synapse after suppression of activity in the ganglion cell. While it is possible either that the synapse may continue to function much longer than the cell body or that the two structures may lose their irritability at about the same time, it is certain that the synapse is not *more* susceptible to anoxia than the perikaryon. In an attempt to determine the rate of oxidative metabolism of different portions of the neuron by the reduction of ferric chloride, Gerard [6] found that the apparent metabolism was much higher in the perikaryon than in neuropil in the brain. While the technic employed is admittedly crude, the results are suggestive.

The available information on neurons of the central nervous system, the axons of which terminate peripherally, also suggests a greater resistance to anoxia of the terminals. The neurons of the lateral horn of the spinal cord undoubtedly cease functioning much earlier, due to anoxia, than do their terminal axons which form the synapses in the stellate ganglion. Similarly, the anterior horn

cells are more susceptible to anoxia than are their terminal axons forming the motor end-plates. These perikarya not only lose function more readily but are also much more susceptible to destruction by anoxia than are the terminals. While the myoneural junction is not a synapse, its functional similarity to the synapse is now well established.

The results of our own investigation demonstrate clearly that the Purkinje cells of the cerebellar cortex can be destroyed by arrest of blood flow and entirely removed without producing evident structural changes in the related synaptic terminals. This has been observed in material following various periods of complete arrest of the circulation of the brain and after varying intervals of survival. The period of survival of our animals would seem to be sufficiently long to bring out pathological changes in, or disappearance of, the boutons terminaux, should such occur following this procedure. Hoff [16] described marked distinctive alterations in the boutons terminaux within 4 days and their disappearance within 6 to 7 days after section of the axon.

While these results indicate that the synaptic terminals on the Purkinje cell are more resistant to damage by arrest of circulation than is the perikaryon, little information is available concerning the quantitative differences in the resistance of the two structures. Moreover, while the correlation between different indices of resistance to anoxia, such as loss of function and permanent morphological damage, is usually good,[6] direct evidence on the relative rapidity of loss of function of synapses and perikarya in the brain is lacking. In general, there is also close correlation between resistance to anoxia and metabolic rate.[6] One cannot overlook the possibility that different synapses in the brain may show great differences in resistance to anoxia in the same way that different neurons show such differences.

The results of this investigation are also of interest, incidentally, in relation to the much debated problem of contiguity or continuity at synapses. Many authors, especially Cajal,[17] championed the view that there is no continuity across synapses. This has been questioned by a number of investigators, a recent supporter of structural continuity across the synapse having been Tiegs.[18] The fact that the synaptic terminals on the Purkinje cell retain their normal structure after disintegration and disap-

pearance of the neuron may be taken as evidence against structural continuity across the synapse.

The hypothesis that the synaptic ending is the most sensitive to anoxia of the various portions of the neuron has been widely accepted despite the lack of conclusive confirmatory evidence. While accurate data on the relative metabolic rates and resistance to anoxia of different parts of the nerve cell are not yet available, the evidence thus far would suggest caution in accepting the traditional view.

Conclusions

1. Complete temporary arrest of the circulation of the brain results in disintegration and removal of the Purkinje cells of the cerebellar cortex, but does not alter the morphological character of the associated boutons terminaux.

2. The relation of this observation to the problem of the relative resistance to anoxia of different portions of the neuron is discussed.

Note: We should like to express our appreciation to A. T. Rasmussen for his kind advice and assistance.

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DESCRIPTION OF PLATE

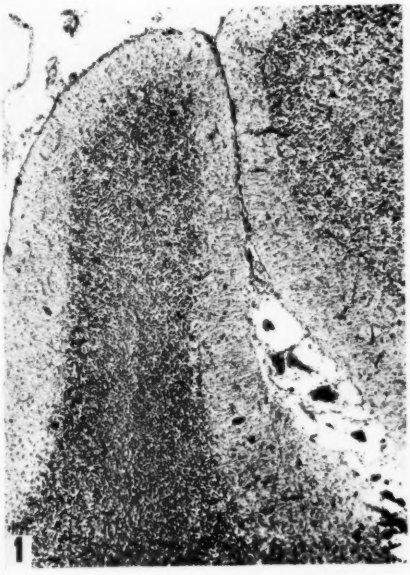
PLATE 133

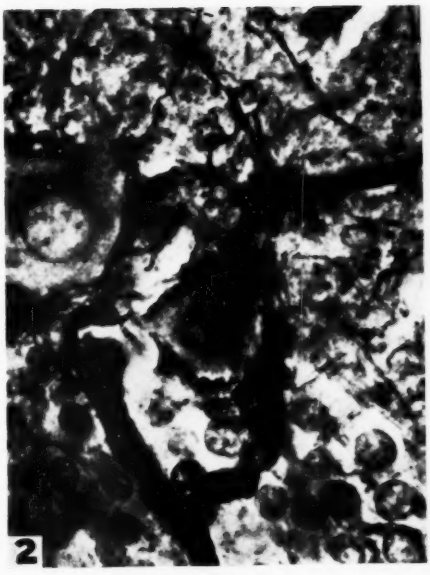
FIG. 1. Photomicrograph of the cerebellar cortex of dog No. 13, stained with hematoxylin and eosin. This illustrates the disappearance of Purkinje cells resulting from 8 minutes of arrest of the circulation of the brain. × 85.

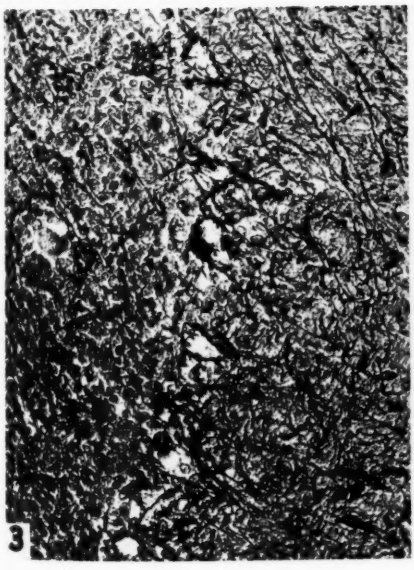
FIG. 2. Photomicrograph of the cerebellar cortex of a normal dog, stained by the Cajal block silver method. This illustrates the normal boutons terminaux on the Purkinje cell. × 860.

FIG. 3. Photomicrograph of the cerebellar cortex of dog No. 13, stained by the Bodian silver method. The animal was subjected to 8 minutes of arrest of the circulation of the brain. The Purkinje cells have disappeared but the baskets of nerve fibers surrounding them persist. × 380.

FIG. 4. Photomicrograph of the cerebellar cortex of dog No. 24, stained by the Cajal block silver method. The animal was subjected to 7 minutes of arrest of the circulation of the brain and survived for 11 days. The Purkinje cell has completely disintegrated and disappeared. Normal boutons terminaux persist in the basket of nerve fibers surrounding the site of the disintegrated Purkinje cell. × 940.







Kabat and Schadewald

Relative Susceptibility to Anoxia

APPENDICEAL OXYURIASIS *

Its Incidence and Relationship to Appendicitis

L. L. Ashburn, M.D.

(From the U. S. Public Health Service, Division of Pathology, National Institute of Health, Washington, D.C.)

Studies on the incidence of appendiceal oxyuriasis (enterobiasis) and the possible causal relationship of this organism to appendicitis have appeared with increasing frequency since 1900. Stimulation of interest in this subject is generally credited to the work of Still [1] and Metchnikoff [2] who emphasized the probable relationship of appendicitis and intestinal helminthiasis.

The incidence of appendiceal oxyuriasis, as reported by different investigators, varies from 0 to 100 per cent. This marked variation may occur from the same country or in the report of one author on two or more series of cases. Crile [3] did not find a single case in the material from 1,000 appendectomies whereas Fischer [4] found 46 positive cases in 110 and Nicolaus [5] found all of 5 surgically removed appendices to be positive. Aschoff [6] in one series found oxyurids in 14 of 78 specimens but in another series [7] of 1,000 appendices oxyurids were found in but 2.

The life history of *Enterobius* (*Oxyuris*) *vermicularis* and the mechanism of human infestation make it reasonable to expect that the incidence of oxyuriasis should vary when reports are based on different races or race groups. However, much of the confusion results from the small number of cases in the various series reported, failure to consider the age and sex factors, and the varying methods used to determine the presence or absence of the worms. Gordon's [8] report based on a large number of cases is one of the few that records adequate pertinent data concerning age and sex. From his rather complete review of the literature, he concluded that "appendiceal oxyuriasis occurs the world over though with varying frequency." Since a detailed listing of the varying incidence figures for Europe would serve no useful purpose, only the averages as compiled by Gordon [8] will be given. For Great Britain the reported incidence is 18.5 per cent; for France,

* Received for publication December 2, 1940.

11.9 per cent; and for continental Europe, 3.7 per cent for surgical, and 16.5 per cent for autopsy specimens.

The American literature, although less voluminous than the European, also shows this marked variation in incidence. Cecil and Bulkley [9] found 20 (13.5 per cent) positive cases in 148 appendices from children. Crile[3] did not record a single case in 1,000 appendices. Deaver[10] and Hanley[11] each found 1 (0.2 per cent) appendix containing oxyurids in series of 500 cases. Erdmann [12] found 4 appendices infested with oxyurids; however, it is not clear from his report whether they represent the positives in the entire series of 201, or occurred in the 22 cases of appendicitis among children. Ney [13] found 3 (3 per cent) positive in 100 appendices; Garlough,[14] 4 (4.2 per cent) in 96; Harris and Browne,[15] 22 (18.2 per cent) in 121; Beck,[16] 35 (2.04 per cent) in 1,718; Goodale,[17] 101 (6.2 per cent) in 1,639; Bell,[18] 15 (10.9 per cent) in 138; Warwick,[19] 45 (1.9 per cent) in 2,344; and Botsford, Hudson and Chamberlain,[20] 71 (5.3 per cent) in 1,343. Gordon [8] in 1931, reporting on 20,969 appendices, found 221 (1.05 per cent) which contained oxyurids on histological examination. In 1933,[21] reporting on an additional 5,082 appendices, he records 90 positive cases, giving an incidence of 1.19 per cent for the entire series of 26,051. Gordon's report, in contrast to most of those referred to above, gives age and sex grouping for both the positive and negative appendices. Comparison of percentages of incidence is of value only if allowance has been made for age and sex.

Material and Methods

From May 1, 1936 to January 11, 1939, 2,616 surgically removed appendices were received for diagnosis. Of these, the lumen was completely obliterated in 91. Ninety-two had been longitudinally opened by the surgeon. Twenty-four were improperly fixed and in 92 cases age and sex data were lacking. These 299 appendices were excluded, leaving a total of 2,317 for use in this study.

The specimens were received from the United States Public Health Service hospitals, located mainly along the east and west coast, and from hospitals of the United States Indian Service. At the former sources, the patients were mainly American seamen or United States war veterans, and at the latter they were full or mixed-breed American Indians living in midwestern and south-

western parts of the United States or in Alaska (Eskimos and Aleutians).

The appendices were fixed in a 4 per cent aqueous solution of formaldehyde for 24 hours or longer, and representative blocks were taken from the proximal, mesial and distal thirds for paraffin embedding. The contents of the remainder of each appendix, in 1,319 cases, were expressed into a small vial containing a 4 per cent aqueous solution of formaldehyde and examined later under a dissecting microscope for the presence of oxyurids. In many cases contents could not be expressed. In some others the amount obtainable by this method was considered inadequate for a satisfactory examination.

Duplicate sections were routinely made of the embedded material and one each stained by the Romanowsky and van Gieson methods. When only a few worms were present they were found in only one level. This fact emphasized the importance of examining the contents of the unembedded portion of each appendix. By this procedure it was possible to determine the number of positive cases that are missed when histological examination alone is relied upon.

More than half of the histopathologic diagnoses were made by me. Although the remainder were made by three other members of the divisional staff, the criteria for diagnosis had been standardized so that no difficulty was experienced in placing a given appendix under its proper diagnostic heading.

In order to make certain comparisons, to be discussed later, the sections of appendices were classified in the following three groups: "contracted," "open and empty," and "open and full." An appendix with a lumen less than 2 mm. in diameter was placed in the first group. If the lumen was greater than 2 mm. ("open"), it was placed in the second or third group, depending on the presence or absence (lost during preparation) of fecal contents.

Results

The Effect of the Method of Examination on the Percentage of Incidence

The incidence of appendiceal oxyuriasis, as shown by different reports, has been based on gross inspection, on examination of stained sections or on microscopic examination of the entire ap-

pendiceal contents. Only by the latter method can a correct rate be calculated. By histological examination, Gordon [21] found oxyurids in 1.19 per cent and Warwick [19] in 1.9 per cent of their cases; and by microscopic examination of the removed appendiceal contents, Goodale [17] found 6.1 per cent and Beck [16] 2.03 per cent positive. These percentages indicate only the relative effectiveness of the two methods since the effect of age and sex on incidence is not shown in these figures. Bell's [18] reported incidence of 10.9 per cent is based on examination of contents, but he does not state whether or not microscopic examination was done.

In this study oxyurids were found in 133 (10.1 per cent) of 1,319 specimens from which appendiceal contents were expressed. Of this number, 28 were positive also in section, leaving 105 (57 per cent of the 184 total positives), which would have been missed if histological examination alone had been relied upon. This would have reduced the total incidence, for the series of 2,317 cases, from 7.9 per cent to 3.41 per cent.

In routine paraffin embedding, sectioning and staining, the contents are often lost from one or more of the three blocks. This is another factor productive of the lower incidence obtained by this method of examination. In this series there were 108 appendices, the lumina of which were "full" at all three levels. This group showed 5.56 per cent positive for oxyurids. There were 182 with two levels full and one empty, and 182 with one level full and two empty. These showed 5.49 per cent and 1.65 per cent positive, respectively.

Gordon's [8] observation that when oxyurids were present in one block "the other two blocks were seldom completely devoid of worms" does not agree with the positive cases of this series. There were 34 positive appendices in which the lumina of all three blocks contained fecal material. Of this number only 4 (11.8 per cent) were positive in all three blocks; 7 (20.6 per cent) were positive in two blocks; and 23 (67.6 per cent) were positive in one level only. When all levels contained worms, the average number per block was 4.17; when two blocks were positive, the average for the two blocks was 2.15; and when only one level contained oxyurids, the average number was 1.48. As would be expected, these figures show that the probability of finding more

than one block positive is roughly proportional to the total number of worms in the appendix. It also emphasizes the necessity of microscopic examination of the entire appendiceal contents in order to get an accurate incidence rate.

Race, Age and Sex

Generally, the figures for incidence for European countries are higher than those for the United States. This greater reported incidence is probably partly due to environmental conditions and race habits. In this study there is a prominent difference in incidence among the white population (seamen and veterans) of the United States, Indians of the United States, and Eskimos and Aleutians. In the former (Table II) the incidence is 2.88 per cent; in United States Indians, 10.04 per cent (Table III); and in Eskimos, 23.91 per cent (Table IV). These figures are not adjusted for age and sex. However, when these are corrected for sex and the age period of 12 to 41 years is used, the difference is equally prominent. For this age period, the incidence for white females is 3.64 per cent, for Indian females, 10.6 per cent, and for Alaskan females, 27.3 per cent. In Tables II, III and IV, both negative and positive cases are listed to show the effects of age, sex and race on incidence. In addition to the races mentioned, the total series (Table I) includes 1 Japanese, 1 Filipino, 10 Mexicans and 40 Negroes. The number of cases in the latter race is too small for reliable analysis; however, the finding of only 1 positive appendix in 40 (2.5 per cent) fits in with the observation of Cram, Jones, Reardon and Nolan [22] that oxyuriasis occurs more frequently among the white population than among Negroes.

Since the effect of age and sex on incidence is comparable for the various races, the entire series is used in the discussion of these factors. It is generally agreed that appendiceal oxyuriasis is most frequent at the younger ages and relatively rare after the fifth decade. In this study the peak incidence occurs in the 7 to 11 year period (19.2 per cent) with a gradual fall to 4.7 per cent for the 27 to 31 year age group and then a sudden rise to 11.2 per cent for the next 5 year period. This secondary peak incidence is present in both white and Indian races, although occurring at a later period among the Indians. In Gordon's [8] study, the highest incidence occurred in the 2 to 6 year period, whereas in our study

TABLE I

Incidence of Appendiceal Oxyuriasis in 2,317 Appendices

Age groups	Males			Females			Both sexes						
								Cases with oxyurids*					
	No.	With oxyurids	Percentage positive	No.	With oxyurids	Percentage positive	No.	H+	H+ Z−	H− Z+	H+ Z+	Total positives	Percentage positive
0–23 mo.	1	0		9	1	11.11	1	0	0	0	0	0	....
2– 6 yrs.	12	1	8.33	9	1	11.11	21	0	2	0	0	2	9.52
7–11 "	40	6	15.00	54	12	22.22	94	1	6	7	4	18	19.15
12–16 "	81	5	6.17	229	34	14.85	310	1	6	24	8	39	12.58
17–21 "	258	12	4.65	285	30	10.53	543	4	5	27	6	42	7.73
22–26 "	253	9	3.56	205	16	7.80	458	5	4	14	2	25	5.46
27–31 "	173	7	4.05	125	7	5.60	298	3	2	9	0	14	4.70
32–36 "	121	9	7.44	94	15	15.96	215	4	3	14	3	24	11.16
37–41 "	107	5	4.67	55	4	7.27	162	1	2	5	1	9	5.56
42–46 "	79	1	1.27	28	5	17.86	107	0	2	2	2	6	5.61
47–51 "	37	1	2.70	20	3	15.00	57	1	1	2	0	4	7.02
52–56 "	27	0	....	3	0	....	30	0	0	0	0	0	....
57–61 "	11	1	9.09	2	0	....	13	0	0	1	0	1	7.69
62–66 "	5	0	....	1	0	....	6	0	0	0	0	0	....
67–71 "	2	0	....				2	0	0	0	0	0	....
Total	1207	57	4.72	1110	127	11.44	2317	20	33	105	26	184	7.94

* H: histological examination + or —.
Z: removed contents examined + or —.

it occurred in the 7 to 11 year group. It is admitted that in our series the number of cases in the younger group is small. However, Cram and associates,[22] by anal swab examination, found the incidence to be higher in the school age (6 to 18 years, 50.3 per cent) than among pre-school children (2 to 5 years, 28.9 per cent). This lower incidence among pre-school children was also

TABLE II

Incidence of Appendiceal Oxyuriasis Among White Beneficiaries of the United States Public Health Service Hospitals

Age groups	Male		Female		Both sexes		
	No.	With oxyurids	No.	With oxyurids	No.	With oxyurids	Percentage positive
(*years*)							
2– 6	1	0	1	0	2	0	...
7–11	2	0	4	0	6	0	...
12–16	6	0	13	2	19	2	10.53
17–21	161	7	27	1	188	8	4.26
22–26	146	2	22	0	168	2	1.19
27–31	90	2	24	0	114	2	1.75
32–36	77	4	13	0	90	4	4.44
37–41	75	2	11	1	86	3	3.49
42–46	62	1	3	1	65	2	3.08
47–51	22	0	5	0	27	0	...
52–56	19	0	2	0	21	0	...
57–61	8	0			8	0	...
62–66	3	0			3	0	...
67–71	2	0			2	0	...
Total	674	18 (2.67%)	125	5 (4.00%)	799	23	2.88

TABLE III

Incidence of Appendiceal Oxyuriasis Among Indians of the United States

Age groups	Male		Female		Both sexes		
	No.	With oxyurids	No.	With oxyurids	No.	With oxyurids	Percentage positive
0–23 mos.	1	0			1	0	...
2– 6 yrs.	10	1	7	0	17	1	5.88
7–11 yrs.	36	6	49	12	85	18	21.18
12–16 yrs.	74	5	204	30	278	35	12.59
17–21 yrs.	81	4	248	26	329	30	9.12
22–26 yrs.	95	6	166	12	261	18	6.90
27–31 yrs.	63	2	92	5	155	7	4.52
32–36 yrs.	40	4	74	12	114	16	14.04
37–41 yrs.	23	3	41	2	64	5	7.81
42–46 yrs.	9	0	22	3	31	3	9.68
47–51 yrs.	12	1	14	3	26	4	15.38
52–56 yrs.	6	0			6	0	...
57–61 yrs.	2	1	2	0	4	1	25.00
62–66 yrs.	2	0	1	0	3	0	...
Total	454	33 (7.27%)	920	105 (11.41%)	1374	138	10.04

found by Kuitunen-Ekbaum [23] and Chanco and Soriano.[24] Goodale,[17] studying appendices, found for males a higher rate of infestation in the 11 to 20 year group than in the 1 to 10 year period, and the reverse for females. His figures cannot be broken down further for a more direct comparison as to age incidence. Considering the large number of reports on incidence of appendiceal oxyuriasis, it is surprising that so few give consideration to infestation rates by ages. Harris and Browne,[15] Beck [16] and Warwick [19] give ages only for the positive cases.

TABLE IV

Incidence of Appendiceal Oxyuriasis Among Eskimos and Aleutians

Age groups	Male		Female		Both sexes		
	No.	With oxyurids	No.	With oxyurids	No.	With oxyurids	Percentage positive
(*years*)							
2– 6			1	1	1	1	100.00
7–11	2	0	1	0	3	0	.....
12–16	1	0	11	2	12	2	16.67
17–21	6	1	10	3	16	4	25.00
22–26	6	1	16	4	22	5	22.73
27–31	9	3	9	2	18	5	27.78
32–36	2	0	6	3	8	3	37.50
37–41	2	0	3	1	5	1	20.00
42–46	1	0	3	1	4	1	25.00
47–51	1	0	1	0	2	0	.....
52–56	1	0			1	0	.....
Total	31	5 (16.13%)	61	17 (27.87%)	92	22	23.91

Gordon [8] pointed out that it is necessary to correct for age in comparing incidence of appendiceal oxyuriasis between the sexes. He found that for the ages 2 to 46 years, the ratio of positive cases was 1 male to 1.4 females. If his figures are examined in small groups (5 year intervals), there is a considerable variation of this ratio (Table V) ranging from 1 male to 0.81 females, to 1 male to 3.74 females. In our study a similar variation occurs, though to much less extent. The lowest ratio, 1 male to 1.33 females, occurs in the 2 to 6 year group, and the highest, 1 male to 2.41 females, is seen in the 12 to 16 year age period. The ratio of the positives is 1 male to 2.34 females when all cases between 2 and 46 years are included.

This higher incidence in females has been reported by many authors including Fischer,[4] Harris and Browne,[15] Goodale,[17]

Bell,[18] Warwick,[19] and Matsuoka.[25] Frequently, however, the ratio as stated is misleading due to the fact that allowance is not made for an undue proportion of one sex occurring in an age period of high incidence.

Appendiceal Oxyuriasis and Appendicitis

Location of Worms. Gordon [21] and Warwick's [19] studies indicate that appendiceal oxyuriasis is gradually increasing in fre-

TABLE V

Incidence of Appendiceal Oxyuriasis as Related to Sex

Age groups	Author's series	Gordon's series*		
	Ratio of percentage of positive cases, male to female	Percentage positive, male	Percentage positive female	Ratio of percentage of positive cases, male to female
(*years*)				
2– 6	1 – 1.33	9.99	8.11	1 – 0.81
7–11	1 – 1.48	4.43	5.03	1 – 1.14
12–16	1 – 2.41	1.61	3.00	1 – 1.86
17–21	1 – 2.26	0.38	0.87	1 – 2.29
22–26	1 – 2.19	0.27	1.01	1 – 3.74
27–31	1 – 1.38	0.96	0.98	1 – 1.02
32–36	1 – 2.15	0.25	0.55	1 – 2.20
37–41	1 – 1.56	0.34	1.20	1 – 3.53

* Percentages and ratios computed from Gordon's [8] Table I.

quency. This increases the importance of the possible causal relationship of oxyuriasis to appendicitis. Much of the evidence that has been submitted is of a circumstantial nature and cannot be relied upon for definite conclusions. The direct evidence upon which a justifiable conclusion should be based is the demonstration of inflammatory lesions in the wall of the appendix due to parasitic invasion. Oxyurids have been found by many investigators at varying depths in the wall but there is a difference of opinion as to whether the invasion took place preoperatively or postoperatively. Of the 184 appendices in our series that contained oxyurids, 79 were found positive by histological examination. Only one of these showed invasion of the wall. In this case the worm was present in the mucosa just within the margin of a lymphoid follicle, lying in a smooth-walled space. The marginating lymphoid tissue showed prominent pressure condensation of the lymphocytes, but there was no evidence of any inflammatory reaction and hemorrhage was not present. In 65 appendices the worms were present only in the lumen and were not in contact with the mucosa. In 13, one or more oxyurids were in contact

with the mucosa; of these, 7 showed shallow crescent-shaped depressions with from slight to marked atrophy of the surface epithelium; rarely nuclei showed karyorrhexis. Hemorrhage was not seen in any of these, and there was no inflammatory reaction in the underlying lamina propria. Gordon,[21] in 311 positive cases, found 33 in which oxyurids had penetrated to various depths in the wall. In none of these was there any inflammatory reaction in the surrounding tissue. This fact, together with other evidence, led him to the conclusion that invasion had taken place postoperatively. Cecil and Bulkley,[9] Botsford, Hudson and Chamberlain [20] and Askanazy [26] also noted the absence of inflammation around the invading worm. The latter author, however, stated that in a rare case the invading oxyurid dies in the tissue and initiates a proliferative pseudotuberculous reaction. From the photomicrographs he submits to illustrate this process it is impossible to identify the foreign material as an oxyurid. Harris and Browne [15] also found oxyurids in the appendiceal wall, but in their cases associated inflammatory changes were present.

This laboratory repeatedly emphasizes the necessity of immediate fixation of specimens that are to be submitted for histologic examination. This fact is interesting in view of our single example of invasion by an oxyurid. Bearing on this subject is the fact that Beck [16] and Warwick [19] removed the appendiceal contents immediately after operation. On histologic examination they did not find a single appendix showing worms in the wall.

Relationship of Incidence to "Pathologic Type." The evidence most frequently presented by those who deny any relationship between oxyuriasis and appendicitis is the common occurrence of these worms in normal appendices and their low incidence in acute appendicitis. Table VI lists both positive and negative cases by pathologic diagnosis. The incidence of infestation in the normal appendices and in those showing chronic appendicitis is about equal, being 10.9 per cent for the former and 10.2 per cent for the latter. All appendices showing acute or subacute inflammation, with the exception of the acute catarrhal group, had a much lower rate of infestation. The incidence for the acute catarrhal group is 8.1 per cent. Most investigators agree that oxyurids are relatively infrequent in suppurating appendices; however, there is considerable divergence of opinion as to their frequency in

other pathologic types. This is probably due to the non-standardization of criteria for the diagnosis of appendicitis. There have been a few reports showing infestation to be higher in inflamed than in normal appendices. These, however, are in the minority. Innes and Campbell [27] stated that in no case did they find worm infestation in a "healthy appendix."

Activity of Inflammation and Incidence. In this laboratory, chronic appendicitis, from a pathologic standpoint, is divided into

TABLE VI
Pathological Diagnoses and Incidence of Oxyuriasis

	No. appendices	No. with oxyurids	Percentage positive
Normal	55	6	10.91
Chronic	1378	141	10.23
Chronic and acute	225	12	5.33
Chronic and subacute	159	7	4.40
Acute	323	8	2.48
Acute catarrhal	37	3	8.11
Subacute	122	7	5.74
Tuberculosis, carcinoid, appendiceal abscess	18	0	....

two groups: inactive and active. Appendices in the former group show from slight to marked increase in fibrous tissue in the submucosa and serosa, and occasionally scarring of the muscularis. These findings are considered evidence of past damage. The minimum requirement for placing an appendix in the active group is the finding of slight to marked phagocytic activity of the follicular reticulum cells. There is frequently other evidence of chronic activity, such as variable numbers of lymphocytes in the muscularis and serosa. Of the 1,378 appendices that were diagnosed as chronic appendicitis, 479, with 7.1 per cent positive for oxyurids, showed no phagocytic activity of the follicular reticulum cells. The remaining 899 showed slight, moderate or marked phagocytic activity. There were 8.9 per cent positive for oxyurids in the 463 appendices with slight activity, 15.5 per cent positive in the 369 with moderate activity and 13.4 per cent in the 67 appendices showing marked phagocytic activity of the follicular reticulum cells. These figures indicate that in the chronic appendicitis group, appendiceal oxyuriasis occurs more frequently in cases showing an active pathologic process. It should be emphasized, however, that a considerable number of positive appendices

showed no active lesions; also, when chronic appendices were compared with normals (Table VI), the incidence of oxyuriasis was not significantly different. These facts emphasize the fallacy of relying too much on circumstantial evidence.

In none of the positive cases showing inflammation was there any evidence to suggest that the worms were etiologically related to the appendicitis.

Oxyurids and Fibrosis. Rheindorf [28] offered the theory that oxyurids in the appendix cause an increase in connective tissue deposition. This relationship of oxyurids to sclerosis has been denied by Aschoff.[7] In this connection our data are of interest. There were 225 appendices which showed absence of mucosa with fibrous obliteration of the lumen. Of these, 55 showed obliteration of the distal half, and in 170 only the distal third was involved. In this group, oxyurids were present in 6 appendices (2.67 per cent). Since most of the 225 cases were in the chronic appendicitis group (showing 10.2 per cent infestation), the low incidence in this "obliterative" group is ample evidence against the Rheindorf theory.

Local Eosinophilia. There have been a number of authors who have commented on the relation of local eosinophilia and appendiceal oxyuriasis. Fischer,[4] in his study, found that appendices containing the greatest number of oxyurids frequently showed the most marked local eosinophilia; however, he found some with marked eosinophilia and no parasites. Beck [16] stated that in her series local eosinophilia was not significantly increased in the positive cases. Gordon,[21] in a controlled study, found local eosinophilia as often in the negative appendices as in those containing oxyurids. Eastwood [29] came to the same conclusion. His report is based on 73 inflamed appendices and 50 normal ones. The inflamed group included those showing varying degrees of activity; hence local eosinophilia was markedly affected by this factor, which would mask or accentuate any possible relationship between the presence of oxyurids and local eosinophilia.

Since the degree of appendiceal eosinophilia varies with the degree of inflammation, only appendices showing chronic inflammation were used in the comparison shown in Table VII. The degree of eosinophilia was graded by one individual. It was considered possible that finding oxyurids in the section might have

TABLE VII

Appendiceal Oxyuriasis and Local Eosinophilia

Increase in eosinophils	Negative for oxyurids			Positive for oxyurids			
	By histologic examination		By examination of appendiceal contents	By histologic examination		By examination of appendiceal contents	
None	440 (82.2%)		617 (82.2%)	44 (65.7%)		62 (77.5%)	
Slight	75 (14.0%)		93 (12.4%)	16 (23.9%)		15 (18.8%)	
Moderate	18 (3.4%)	17.8%	40 (5.3%)	6 (8.95%)	34.3%	2 (2.5%)	22.5%
Marked	2 (0.37%)		1 (0.13%)	1 (1.5%)		1 (1.25%)	

some psychological effect on the grading, hence a comparison was made between the appendices which were positive in sections and those in which oxyurids were found only by examination of the removed appendiceal contents. The results showed this check on grading to be worth while. Of the appendices positive in section, 34.3 per cent showed local eosinophilia whereas only 22.5 per cent of those positive by the second method of examination showed such an increase.

The controls (negative cases) were also divided into two groups, to determine what effect "chance" would have on the recognition of local eosinophilia. There were 751 appendices which were negative by examination of the removed contents. Of this group, 17.8 per cent showed an increase in eosinophils. Of the remaining 535 negative cases, examined only in section, 17.8 per cent showed local eosinophilia. From this one must conclude that the higher percentage of appendices with local eosinophilia which occurred in one of the positive groups was due to the psychological effect of the observed presence of the worm, when the grading was done.

Local eosinophilia was only 4.7 per cent more frequent in the positive than in negative appendices. This difference cannot be accepted as statistically significant, especially since the difference between the two positive groups (11.8 per cent) was more than twice this figure.

SUMMARY AND CONCLUSIONS

1. In a series of 2,317 surgically removed appendices, oxyurids were found

in 184 (7.94 per cent). Seventy-nine were positive in the sectioned material and in 105, oxyurids were found only by examination of the removed appendiceal contents.

2. Of the 34 appendices showing oxyurids in section and having fecal material in all three blocks, only one level was positive in 23 cases (67.65 per cent), two levels were positive in 7 (20.58 per cent) and all three levels were positive in 4 cases (11.76 per cent).

3. The incidence of appendiceal oxyuriasis was found to be 2.88 per cent for the white beneficiaries of the United States Public Health Service hospitals, 10.04 per cent for Indians of the United States, and 23.91 per cent for Eskimos and Aleutians.

4. The highest incidence occurred in the 7 to 11 year age group, being (for the entire series) 15 per cent for males and 22.22 per cent for females. The decrease in incidence was gradual until the 32 to 36 year period at which a second peak occurs, 7.44 per cent for males and 15.96 per cent for females. Appendiceal infestation is rare after 51 years of age.

5. Infestation is more common in appendices from females than from males. For the 2 to 46 year age period, the ratio is 1 male to 2.34 females.

6. Comparison of infested and control (negative) appendices showed that local eosinophilia is not significantly increased by infestation with oxyurids.

7. Oxyuriasis occurs as frequently in normal appendices as in appendices showing chronic inflammation and more frequently than in acutely inflamed appendices.

8. Of the 79 cases showing oxyurids in the lumen of the sectioned appendix, 13 showed the worm in contact with mucosa; 7 of these showed pressure atrophy of epithelium with formation of shallow crescent-shaped depressions. Rarely there was a little karyorrhectic necrosis, but no inflammation or hemorrhage was found.

9. One appendix showed an oxyurid in the deep part of the mucosa. The lack of inflammation, necrosis or hemorrhage shows that the invasion occurred postoperatively.

10. No case of "appendicitis oxyurica" occurred in this series. *Enterobius* (*Oxyuris*) *vermicularis* is not etiologically related to appendicitis.

NOTE: The author gratefully acknowledges the assistance of J. P. Folan, of the Division of Zoology, who examined the removed appendiceal contents for the presence of oxyurids, and also that of Coey Jones in carding the statistical data.

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CARDIAC LESIONS RESEMBLING ASCHOFF BODIES IN MICE *

SIDNEY EDWARD LENKE, M.D., and LEO LOEWE, M.D.
(From the Laboratories of the Mount Sinai Hospital, New York, N. Y.)

In a previous paper we [1] have described lesions similar to the Aschoff nodules of human rheumatic fever, occurring spontaneously in the hearts of rabbits. This paper deals with spontaneous carditis observed in mice.

Mice used in this investigation received intracerebral inoculations with material from the hearts of patients who had succumbed to acute rheumatic fever. The mice were 40 to 50 days old. A number of the Swiss strain [2] were included and a further group was exposed to X-ray irradiation [3] in an effort to decrease the resistance to virus infection. Neither factor proved important in the results which are to be discussed. Of 203 injected mice, cardiac lesions of varying severity were found in 60 (29.5 per cent). The intensity of the process was arbitrarily graded from 0 to 4 plus. Table I shows the frequency of mild and severe lesions.

TABLE I
Incidence and Degree of Severity of Lesions

	Injected mice		Control series	
	No.	Per cent	No.	Per cent
No lesions	143	70.5	43	67.2
Lesions++++	7	3.5	4	6.3
Lesions+++	11	5.4	2	3.1
Lesions++	21	10.3	6	9.4
Lesions+	21	10.3	9	14.0
Total	203		64	

As in the experiments dealing with rabbits,[1] an attempt was made to relate these lesions to the inoculation. This was futile. In 64 control mice the incidence of cardiac lesions (32.8 per cent) approximated that in the injected group. Data for this group also appear in Table I. Since there were no significant differences in either the total incidence or the severity of the process between the inoculated and control groups, it was necessary to conclude that the cardiac lesions had occurred spontaneously in both. We

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could not demonstrate, however, an acute epizootic such as was described among the rabbits suffering cardiac lesions.

Figures 1 to 8 illustrate the varied pathological findings, comprising in some animals a true pancarditis; with verrucous involvement of the valves; a mononuclear pericarditis; myocardial foci, often perivascular and containing "owl-eyed" cells resembling those seen in human rheumatic fever; and in other animals showing varying degrees of arteritis and periarteritis.

Discussion

Pathological examination disclosed the following similarities in the spontaneous lesions of the rabbit and the mouse, and the rheumatic human lesions: In all three a focal necrosis of the myocardium was noted. The foci tended to be perivascular. The replacement reaction was mononuclear in type with a tendency to "owl-eyed" cells (which some consider pathognomonic of human Aschoff bodies). In the hearts of all three species, endocarditis, valvulitis, pericarditis and arteritis were also observed. In the more advanced lesions reduplication of the supporting tissue of the endothelium was demonstrated by connective tissue stains. In all three, bacteriological cultures with refined aërobic and anaërobic technics failed to disclose bacteria. Specially stained preparations of the heart lesions also proved devoid of organisms. In none of the species has the etiology of the carditis been determined.

For the study of certain human diseases of unknown etiology, observations of similar spontaneous syndromes of lower animals offer an approach to an understanding of the pathology of the human disease. Smith [4] demonstrated the importance of this method. Recently, studies of this sort have given interesting results in the work of Shope [5] and others on the relationship of human and animal influenza. From this point of view interest may be justified in the description of a disease in mice which resembles in form, if not in etiology, the rheumatic pancarditis of man.

Conclusions

1. A spontaneous pancarditis, resembling human rheumatic pancarditis, is described as it has been observed in mice.

2. The implications of this observation from the viewpoint of comparative pathology are discussed.

3. The discovery of these lesions in control animals will prove to be of value to pathologists who attempt to evaluate experimental cardiac lesions in mice.

NOTE: We wish to thank Paul Klemperer and Gregory Shwartzman for their interest and helpful suggestions. We are also deeply indebted to the late Louis Gross for the time which he devoted to the pathological aspect of this work. Impressed with the resemblance of certain lesions to the Aschoff bodies in rheumatic myocarditis, he applied to them the term "Aschoffoid."

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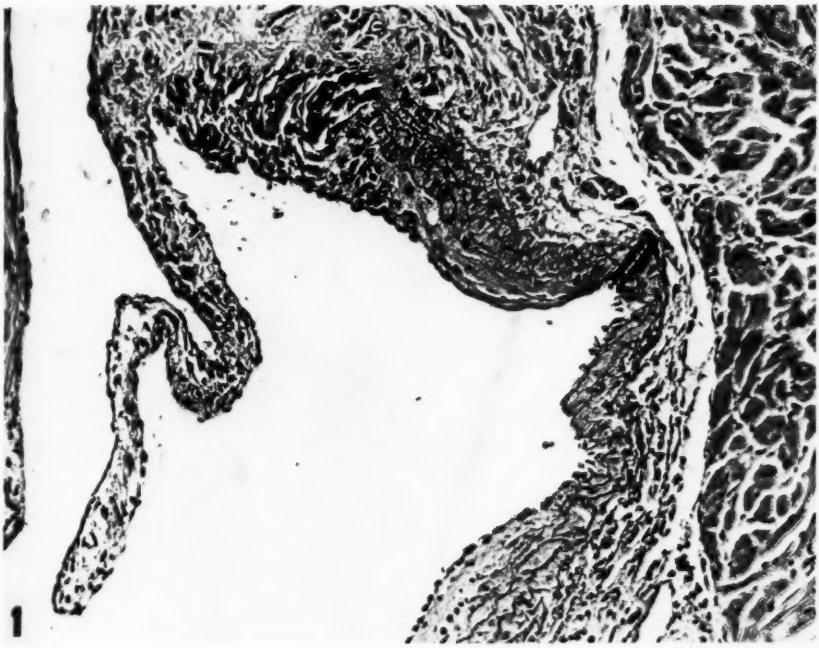
DESCRIPTION OF PLATES

Hematoxylin and eosin staining was used throughout.

PLATE 134

FIG. 1. Mouse No. 198. A lesion in a sinus of Valsalva adjacent to the valve simulates an Aschoff nodule. Interstitial valvulitis is present, most marked at the base. The myocardium shows proliferation of "myocytes," histiocytes with an occasional giant cell and lymphocytes. There is destruction of muscle fibers. × 275.

FIG. 2. Mouse No. 198. Higher magnification of lesion shown in Figure 1. The nodular infiltration consists predominantly of polygonal, often stellate, mononuclear cells. These have large pale nuclei with conspicuous nucleoli, and basophilic cytoplasm. × 625.



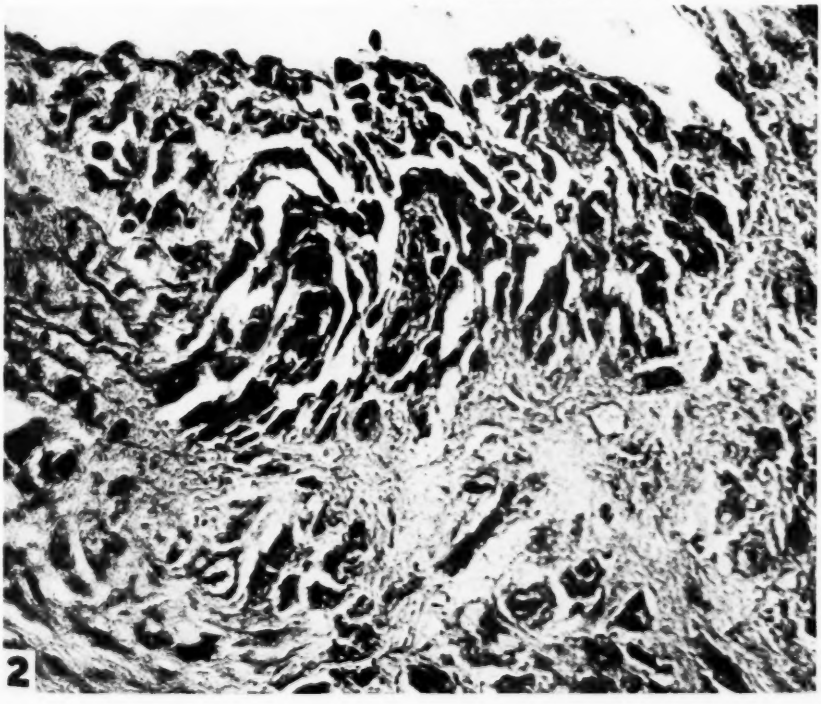


PLATE 135

FIG. 3. Mouse No. 40. Bland verrucous lesion, covered with endothelium, at the root of the aorta in the sinus pocket. × 525.

FIG. 4. Mouse No. 151. Acute arteritis and periarteritis. Periarteritis nodosa-like, vascular lesion. × 450.

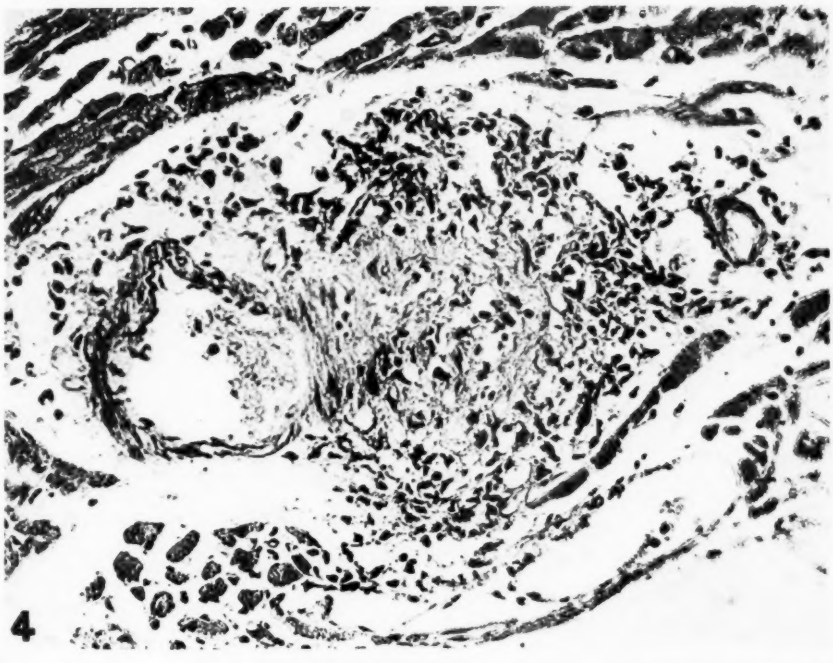
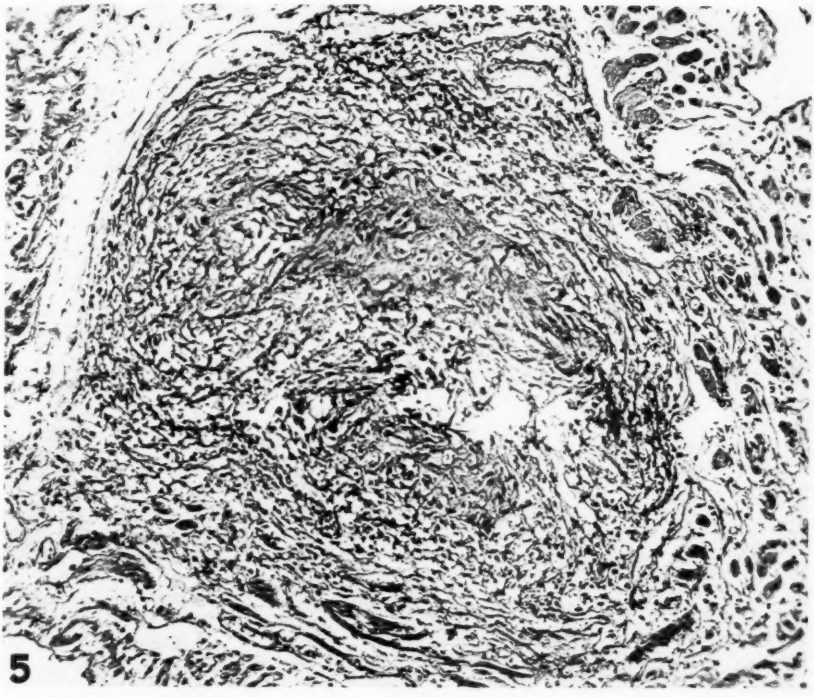


PLATE 136

FIG. 5. Mouse No. 171. Marked necrotizing arteritis. × 290.

FIG. 6 Mouse No. 6. Multiple foci of myonecrosis with early scarring. × 190.



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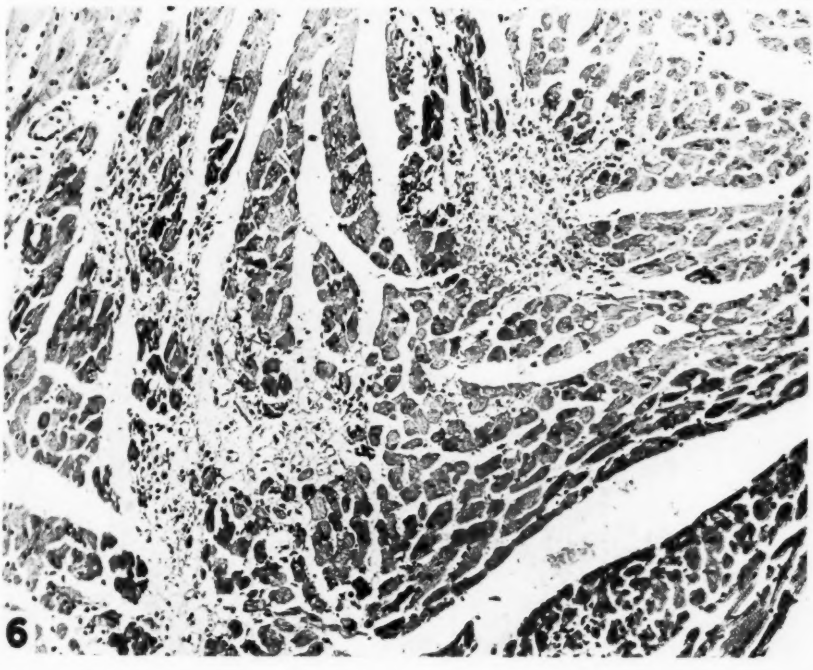

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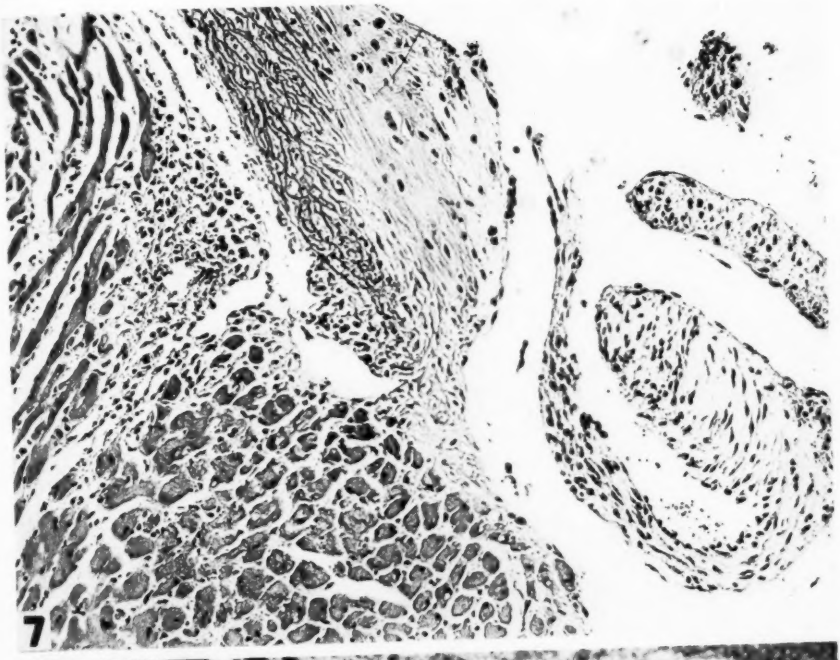
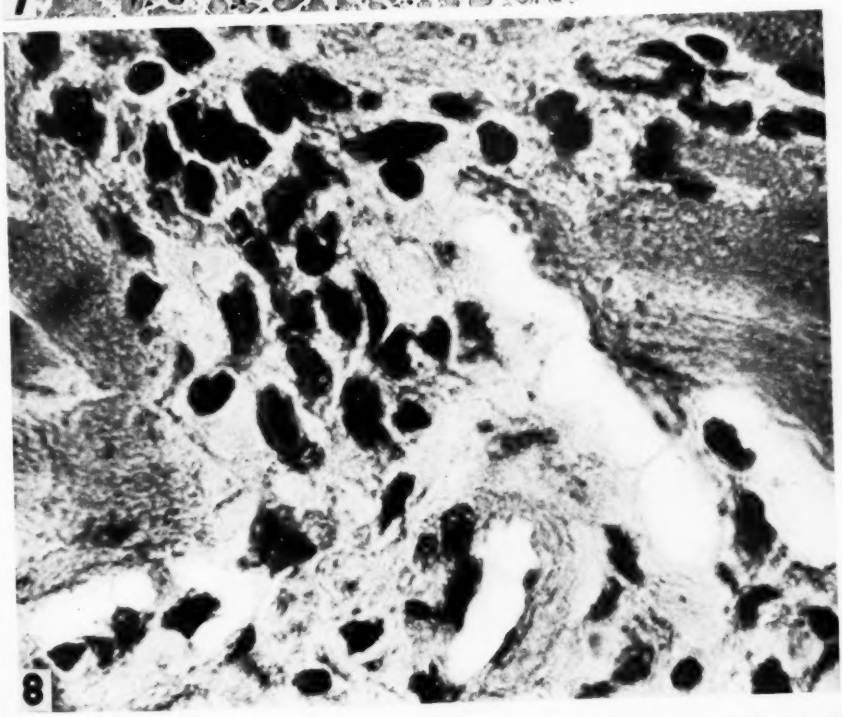
PLATE 137

FIG. 7. Mouse No. 2. Retro-aortic lesion resembling a diffuse Aschoff body. × 230.

FIG. 8. Mouse No. 233. High magnification of segment of perivascular nodule resembling Aschoff body. Interstitial myocarditis. × 1750.





Lenke and Loewe

Cardiac Lesions in Mice

UNIV. OF MICH.

ANTERIOR AND POSTERIOR RHACHISCHISIS *

G. S. Dodds, Ph.D.
(From the Histological Laboratory, School of Medicine, West Virginia University, Morgantown, W. Va.)

Two fetuses exemplifying anterior and posterior rhachischisis have appeared in the embryological collection of the School of Medicine of West Virginia University. Both show clearly the anomaly of the vertebral column, together with the characteristic complex of visceral anomalies associated with it. The condition must be rather rare; I have found reference to only thirty cases in the literature. Yet, it cannot be dismissed casually as a developmental curiosity because it involves an extensive complex of anomalous characteristics, which, in all recorded cases, run true to type. For this reason, it seems worth while to describe the two cases, together with notes on earlier records and comments upon the probable mode of development.

Reports of Cases

Case 1

Male fetus (No. 121) had a menstrual age of 8 months and weighed 2.3 Kg. The head measured 42.5 cm. in circumference. The neck was very short and thick (Figs. 1 and 2). It had club feet (talipes varus), and there were in each jaw four completely erupted incisor teeth. It was secured through Dr. W. B. Scherr, of Morgantown, W. Va.

The Skull. The foramen magnum was unusually large, measuring 27 by 24 mm. (Figs. 2 and 3). Otherwise the skull showed no conspicuous anomalies, except a separation of the bones of the skull cap, characteristic of hydrocephalic infants.

The Vertebral Column. The outstanding anomaly was the complete division into right and left halves of all the cervical and the first seven thoracic vertebrae (Figs. 3 and 5). The two halves of the divided vertebral column were widely separated in their mid-portion, due to strong lateral curvature, so that they bounded a somewhat circular opening about 2 cm. across, lying just below the foramen magnum (Fig. 3). Both halves of the vertebral column also showed strong lordosis (Figs. 4 and 6). The divided vertebrae were decidedly shorter than the corresponding vertebrae

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in a normal fetus. These three factors were responsible for the great shortening of the neck. Each half vertebra had a well developed half arch and half body, between which, on the medial surface, was a notch representing a half intravertebral foramen.

The Central Nervous System. The brain was typical for hydrocephalic infants, with very large lateral ventricles enclosed by greatly distended, thin walls (Fig. 2). The spinal cord was not divided in the region of the divided vertebral column, but was expanded laterally to form a discoid enlargement occupying the circular opening between the two halves of the vertebral column. The spinal nerves radiated from this expansion to their respective vertebral foramina.

The Thoracic and Abdominal Viscera. The viscera showed conspicuous anomalies characterized by extensive ectopia of abdominal organs into the thorax (Fig. 2). On the right side, the diaphragm was complete except for a slit about 1 cm. long. The left side was practically without diaphragm. The pericardium had, on the left side, a hole about 1 cm. across. Thus, pleural, pericardial and peritoneal cavities were in communication with each other.

The heart and lungs were at their usual level above the diaphragm, but lay wholly to the right of the mid-plane of the body and in the ventral half of the thorax. The mediastinum lay obliquely, with its ventral and caudal margins well to the right of the mid-plane. The stomach and the greater part of the small intestine lay in the right pleural cavity, occupying the dorsal half of the right side of the thorax. The stomach was partly in the mediastinum and partly attached to its right side. The esophagus was short. At a little distance above the level of the diaphragm, the small intestine crossed from the right to the left side of the body, and thence coursed to the lower abdominal region. The large intestine was poorly developed.

The left pleural space was occupied largely by about one-third of the liver which entered through the opening in the diaphragm. The spleen lay in the extreme cephalic end of the left pleural space, attached to the left side of the mediastinum. A narrow spatulate lobe of the liver entered the right pleural cavity through the small slit in the diaphragm.

The great omentum was present as a serous sac lying between

the stomach and the right lung. Its attachments were to the right side of the mediastinum and to the greater curvature of the stomach. Otherwise, the serous relations of the abdominal viscera were so distorted that they cannot be designated in conventional terminology.

Case 2

Full-term female fetus (No. 53) weighed 4.3 Kg. It was secured through Dr. A. D. Hunger, of Point Marion, Pa. In all essential features of the complex of anomalies, it was similar to case 1, differing only in details and in external appearance. The head was of normal size. The neck was very short and thick. From the lower occipital region and the short neck there arose a large, pendulous, skin-covered meningeal sac about 12 cm. long and 10 cm. wide (capacity about 200 cc.), hanging to about the tenth thoracic segment (Fig. 7).

The Skull. The skull had no evident gross anomalies, except that the foramen magnum was very large, measuring 4.7 cm. in anteroposterior diameter by 3.0 cm. in width (Figs. 7 and 9). Its unusual expansion was in dorsal and lateral directions. Its ventral edge was in the usual position. Its ventral portion communicated with the spinal canal; its dorsal portion opened above the vertebral column, and through it the meningeal sac protruded (Fig. 7).

The Vertebral Column. There was complete division into right and left halves (as in case 1) of all cervical and the first thoracic vertebrae. The two halves were divergent and well separated, leaving between them a somewhat circular opening about 1 cm. in diameter (Fig. 8). There was lordosis in this region and the individual vertebrae were not of normal length.

The Central Nervous System. The brain was of about normal size and form. The cerebellum was represented by a disintegrating mass, of about the usual size for the organ, enclosed by a meningeal covering. It protruded by about half its diameter through the upper part of the foramen magnum into the meningeal sac (Fig. 7). The cervical spinal cord was conspicuously malformed in that it simulated somewhat the cross-sectional form of the medulla oblongata, with a thick floor of nervous tissue and a thin, broad roof of non-nervous tissue. In fact, the medulla oblongata and the cervical portion of the cord together appeared like an extended medulla. The fourth ventricle was directly continuous, without decrease in size, with the greatly expanded central canal of the cervical cord, forming a continuous cavity about

1.5 cm. wide by 2.5 cm. long. The actual boundary between medulla and cord was at about the usual level with reference to the foramen magnum, as indicated by spinal and cranial nerves and as shown by microscopic sections.

It was from the thin roof of this part of the cord, at about the level of the fourth cervical nerves, that the meningeal sac arose, by a passage measuring about 1.5 cm. in lateral extent by 0.5 cm. in height (Fig. 7). The sac was covered externally by skin, inside which were the spinal meninges. Though microscopic sections were studied from different regions of the sac as well as from the cervical spinal cord, it was not determined with certainty whether the layer lining the sac was an extension of the roof plate of the spinal cord or was derived from the meninges.

There was an anomalous filament of nervous tissue, about 5 mm. long by 0.5 mm. thick, extending ventrad from the floor of the cervical cord at about the level of the fourth cervical nerves. It occupied the center of the circular opening between the two halves of the vertebra. Its basal portion was of gray matter, continuous with the gray matter of the cord; from its more distal portion arose several groups of medullated axons which could not be traced far. The possible significance of this structure will be discussed later.

The Thoracic and Abdominal Viscera. The anomalies of these organs (Fig. 7) were of the same general nature as in case 1. The diaphragm was almost wanting on the left side, but was complete on the right. The pericardium was incomplete on the left side, having a hole about 1.5 cm. in diameter. The right pleural sac was normally closed, but the left pleural sac, the pericardial cavity and the abdominal cavity were in free communication.

The heart and lungs were at the usual level above the diaphragm, but were displaced, together with the mediastinum, into the right side of the thorax. The spleen was high in the left side of the thorax. About one-third of the liver extended into the left thorax through the large opening in the diaphragm. The stomach was just above the level of the diaphragm; the esophagus reached the stomach through the posterior mediastinum, but entered it on its caudal side; the small intestine (165 cm. long), except for the pyloric end of the duodenum, lay in the abdominal region. The large intestine was well developed (about 20 cm. long) and ab-

normally placed, in that from its origin in the lower left abdominal region it coursed almost directly cephalad to the upper end of the thorax and thence directly caudad to the anus. The ectopic abdominal organs occupied not only the left side of the thorax, but had encroached to a considerable extent upon the right side, leaving much less than half the thoracic space for the usual thoracic organs.

The great omentum was recognizable as a small serous sac above the diaphragm with connections to stomach, spleen and large intestine. The mesentery of the small intestine was of about normal form, but the other serous connections of the alimentary organs were greatly distorted.

Discussion

The Occurrence of the Anomaly

Though ***rhachischisis*** and ***spina bifida*** in their ordinary forms are very common anomalies of the vertebral column and spinal cord, the complete division of a series of vertebral segments into widely separated right and left halves is relatively rare.

In *A Reference Handbook of the Medical Sciences** is pictured a vertebral column which shows this anomaly. The illustration is from specimen No. 831 in the Warren Anatomical Museum of the Harvard Medical School. In a personal communication from the curator of the Museum, I have received a brief description of this fetus by Dr. Isaac F. Galloup, 1858. This clearly portrays the anomalies of the vertebrae and viscera which characterize this condition. I have found no other case described in American literature.

Gruber (1926) gives abstracts of 17 cases described by various authors, the earliest in 1824. To these he adds 2 cases from his own observations. Feller and Sternberg (1929 and 1934) add 6 more from the literature and describe 3 others. In all but one of these cases, the cervical and upper thoracic vertebrae were involved, the exception, listed by Gruber (from Reinke, 1877), having the division in the lumbar region. Adelmann (1920) describes a similar lumbar anomaly in a calf.

* William Wood & Co., New York, 1923, ed. 4, 7, figure 4552.

The General Nature of the Anomaly

It appears, from consideration of the several recorded cases, that the two described herein are typical and that the anomaly is not simple, but includes the following complex of anomalous features:

1. The affected vertebrae (usually the cervical and upper thoracic) are completely divided (both arches and bodies) into right and left halves which are widely divergent from each other (Figs. 3, 5 and 8). This condition is fundamentally different from rhachischisis of the ordinary sort in which only the arches are divided.

2. The neck is very short (Figs. 1, 2 and 7). This condition must not be confused with the shortened neck of the ordinary anencephalic or craniorhachischitic fetus, which is due to a quite different defect.

3. In probably all of the recorded cases, there is extensive displacement of abdominal viscera into the thorax (Figs. 2 and 7). The displacement of abdominal viscera into thoracic levels is, in some cases, associated with incompleteness of the diaphragm and the pericardium, while in other cases the diaphragm is complete and the displacement is by way of the posterior mediastinum.

4. Very frequently some division of the alimentary canal is in intimate relation with the spinal cord in the region of the divided vertebrae. Almost any segment of the gut may be involved. Sometimes a loop of the gut passes through the cleft vertebrae and a segment (frequently the stomach) lies dorsad to the vertebral column. There have been observed various forms of patent connections between gut and neural groove, non-patent diverticula and fibrous connections; while some cases show no demonstrable connection of any kind.

5. In the majority of recorded cases, the neural tube is unclosed as in ordinary rhachischisis, giving rise to myeloschisis with its characteristic area medullovasculosa. Various forms of anencephalia and acrania are also of frequent occurrence. But nonclosure of the neural tube is not a necessary part of the anomaly, for less frequently there has been recorded complete closure, with the skin completely covering the mid-dorsal region of head and body. The head may be of normal form and size; or it may be hydrocephalic; or there may be meningocele.

6. The spinal cord, or the open neural groove in the affected region, may be either single or divided into right and left halves; or it may be variously deformed.

Ordinary rhachischisis does not involve any accompanying complex of visceral anomalies; anterior and posterior rhachischisis seemingly always involves ectopia of abdominal organs into the thorax, frequently with incompleteness of the diaphragm. This anomaly of the diaphragm should not be confused with simple congenital hernia of the diaphragm, a much more common condition. This latter condition is well illustrated by Liebow and Miller (1940) who also give a good bibliography. In simple congenital diaphragmatic hernia, the distortion of the digestive organs and serous membranes (mesenteries and omenta) is much less radical than in anterior and posterior rhachischisis; and the ectopic abdominal organs frequently may be restored to their abdominal position by operation. The two types, while having much in common, are in reality fundamentally different in their nature and mode of genesis.

Both of the cases here reported exhibit fully the essential features of the anomaly. Both belong to the type with fully formed head and enclosed spinal cord. In neither is the spinal cord divided. In neither is any connection observed between alimentary canal and neural tube, though in case 2 the nervous projection from the ventral side of the cervical spinal cord may be a remnant of a former connection. Both cases belong to the type in which the displacement of abdominal viscera is associated with incomplete diaphragm; the misplaced viscera lie directly within the pleural cavities, not in the posterior mediastinum.

Concerning Terminology

Inasmuch as this anomaly involves an extensive and definite complex of congenital structural defects, it should have a distinctive name. It has frequently been called "spina bifida." But that is hardly a suitable name because, in its strict application, as defined in dictionaries and encyclopedias and as commonly used in textbooks, it designates those conditions in which there is a meningeal protrusion through a rather minor defect in the vertebrae. On the other hand, the application of the term has been so loose and so varied that its use in this case would not be at all defini-

tive. Nor is "rhachischisis" in its ordinary meaning applicable. It has sometimes been designated as "Wirbelkörperspalte," which is a fairly descriptive term, but hardly one which might come into general use. "Vertebra bipartita" has apparently not been used with exactly this application, though it seems suitable.

Probably the best terms (though somewhat cumbersome) are "anterior and posterior spina bifida" and "anterior and posterior rhachischisis." Both of these have been used, and I believe that neither has been applied to any other form of cleavage of the spine. Of the two terms, I have chosen the latter as the more suitable, because "rhachischisis" has not been used with so many different applications as has "spina bifida." In this paper the phrase "anterior and posterior rhachischisis" carries with it not only its primary significance (division of vertebral arches and bodies), but also implies the entire complex of visceral anomalies which seem to be universally associated with it.

The Probable Course of Development of the Anomaly

The common types of spina bifida and rhachischisis result from varying failure of the neural tube to close. On the other hand, anterior and posterior rhachischisis involves failure of the paired sclerotomes to unite, the failure occurring either with or without proper closure of the neural tube. Consequently, this anomaly can in no sense be considered an extreme manifestation of either spina bifida or rhachischisis, but rather an anomaly of a different type.

It would seem, further, that non-fusion of sclerotomes is determined by forking (doubling) of the notochord, inasmuch as notochordal rests have been observed in each half of such vertebral bodies (Feller and Sternberg, 1929). Several writers have contended that the forking of the notochord results from anomalous behavior of the primitive node, and that the anomalous connection, sometimes patent, between gut and neural tube is a persistent neurenteric canal. Adelmann (1920) and other writers support this view by reference to Hertwig (1892) and other experimenters who have produced, in amphibian embryos, duplications of axial structures and non-closure of neural tube (all loosely called "spina bifida"). These results were brought about by experimental procedures which were timed to prevent normal development in the region of the blastopore.

Study of these earlier papers shows that the experimental defects produced in amphibian embryos are by no means identical with the human anomalies under consideration. Confusion on this point has arisen because both sets of conditions have been loosely designated as "spina bifida." Moreover, recent experimental work has presented strong evidence that the avian and mammalian primitive streak and neurenteric canal are not derived from the amphibian blastopore. Nevertheless, there are suggestive similarities between the two sets of structures, and recent experimental work gives unexpected support to the view that anterior and posterior rhachischisis may indeed result from anomalous behavior of the primitive node and the neurenteric canal.

According to this recent conception (Jacobson, 1938; Weiss, 1939; and others) the primitive node is a restricted area through which there invaginate two lateral areas of presumptive notochordal material which unite just cephalad to the node to form the definitive notochord. In a somewhat similar manner, the neural plate is formed by the confluence of two lateral areas of presumptive neural material. By this concept, the neurenteric canal, a temporary opening through the node, lies between the two converging streams of notochordal material which normally unite just cephalad to it. So much seems clearly established by experimental procedures.

On this basis, it seems safe to assume that, in rare cases, as an anomaly, an unusually large neurenteric canal, or one which persists too long, might produce doubling of the notochord by preventing the union of the two notochordal streams. Two notochords, separated by a considerable interval, might well prevent the normal union of the paired sclerotome masses, thus producing a series of vertebral bodies about each notochord. The interval of separation would also prevent the union of right and left halves of the neural arches, even though the neural tube might have undergone normal closure. In like manner, the two neural streams might also fail of fusion, thus producing two spinal cords or one malformed cord.

The fact that it is usually in the cervical and upper thoracic regions that such division of vertebrae occurs, correlates well with the probable location of the neurenteric canal during its

normally short existence. There is increasing agreement that the primitive node, at the time of its first appearance, is located in what corresponds to the posterior cephalic region, whence it recedes in a caudal direction as the notochord is spun through it. The human neurenteric canal makes its appearance in the primitive node shortly after the formation of the first pair of somites, and it normally closes after about six pairs have been formed (Bartelmez, 1926, and others). Inasmuch as the somites take definite form at some little distance cephalad to the primitive node, the neurenteric canal, during its period of normal patency, must lie in the cervical or upper thoracic regions, the very levels at which divided vertebrae are common observed. A persistent neurenteric canal is strongly indicated in those cases of anterior and posterior rhachischisis in which there is a patent connection between gut and open spinal cord; a partial persistence is suggested by the diverticula and fibrous connections found in others, or by the nervous appendage observed in case 2.

Since the division of the vertebrae is usually limited to cervical and upper thoracic levels, such anomalous neurenteric canal is clearly left behind in that region instead of receding caudad along with the primitive node. The retention of this union in the cervical region is probably due to attachment to structures which do not normally recede as does the primitive node or the abdominal and thoracic viscera. In the several described cases of anterior and posterior rhachischisis, the peculiar ectopic positions of the abdominal organs are clearly indicative of retention rather than of herniation into the thorax after a normal descent. The anomalous connection between gut and cervical neural tube would prevent the normal recession of other parts of the entodermal tube and its associated mesodermal structures. Faulty development of diaphragm, pericardium and other serous membranes would also result.

On the other hand, it is commonly believed that in simple congenital hernia of the diaphragm, the ectopic abdominal organs have entered the thorax by actual herniation from the abdomen, probably not earlier than the eighth week (Liebow and Miller, 1940). Herein lies a significant distinction between the two types of visceral ectopia.

In general, it would seem that the entire complex of anomalies

finds its most reasonable explanation in anomalous behavior of the neurenteric canal, an explanation which serves to tie together the striking anomalies of skeleton, nervous system and body viscera.

Summary

The two fetuses described in this paper had the following anomalies which are characteristic of the general complex designated here as "anterior and posterior rhachischisis":

1. The neck was very short and thick.

2. The shortness of the neck was due to the complete division into right and left halves of all of the cervical vertebrae and some of the thoracic vertebrae.

3. The diaphragm was practically wanting on the left side. There was a good-sized opening in the left side of the pericardium between the pericardial cavity and the left pleural cavity.

4. A large portion of the liver, the spleen and portions of the abdominal alimentary tract were in the thorax, crowding the heart and lungs wholly to the right side of the median plane.

Each fetus had other external and internal anomalies which are not considered as part of the general complex comprising anterior and posterior rhachischisis.

There is included a discussion of about thirty previously described cases, together with comments upon opinions of earlier writers as to the mode of origin of the anomaly, interpreted in the light of certain recent experimental embryological work. Anterior and posterior rhachischisis is compared with the ordinary forms of spina bifida and rhachischisis, and with the common congenital diaphragmatic hernia.

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DESCRIPTION OF PLATES

Plate 138

Fig. 1. Case 1. External form. Photograph after preservation in solution of formaldehyde.

Fig. 2. Case 1. Photograph after sectioning in the sagittal plane, showing the absence of neck, the expanded skull and the distended cerebral hemispheres characteristic of hydrocephaly, the somewhat enlarged foramen magnum, the spinal canal (spinal cord removed) connecting with the foramen magnum, the undivided lower thoracic vertebrae, the divided upper thoracic and cervical vertebrae (the divided vertebrae are not seen in the plane of this section on account of their strong lateral curvature as shown in Fig. 5), the large liver partly in the thorax, the incomplete diaphragm partly subdividing the liver, and the stomach lying between the thoracic liver and the vertebral column.

Fig. 3. Case 1. Dissection to show division of vertebral column in an oblique view. The two halves of the divided vertebrae bound a roughly circular opening through which are seen the base of the skull and the foramen magnum. The expanded portion of the spinal cord occupied this opening, giving off nerves radially through foramina in the encircling half vertebrae.

Fig. 4. Case 1. Lateral view after dissection. The strong lordosis of the divided part of the vertebral column and the pronounced lateral curvature (see Fig. 3) bring the base of the skull close to the upper thoracic vertebrae. Shortening of the segments in the divided region is also shown.

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PLATE 139

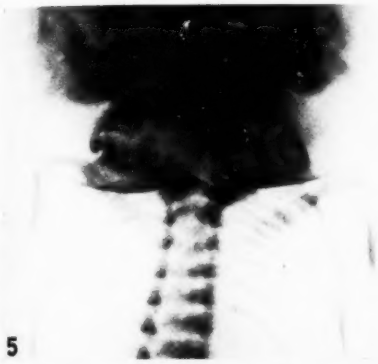
FIG. 5. Case 1. Anteroposterior roentgenogram, showing forking of vertebral column in mid-thoracic region. The effective length of the vertebral column is reduced by strong lateral curvature of the two halves.

FIG. 6. Case 1. Roentgenogram of lateral half of fetus, showing the extent of cervical and thoracic vertebrae. The strong lordosis has brought the spinous processes of the divided thoracic vertebrae close to the base of the skull.

FIG. 7. Case 2. Photograph after sectioning in the sagittal plane. There are many features similar to those of case 1 (Fig. 2): absence of neck; very large foramen magnum; divided cervical vertebrae; displacement of abdominal viscera (liver, large intestine and stomach) into the thorax through a large opening in left side of diaphragm. There is a very large meningocele covered with skin, arising by a narrow passage from the thin roof of the cervical spinal cord immediately opposite the divided vertebrae.

FIG. 8. Case 2. Anteroposterior roentgenogram showing division of cervical vertebrae. The irregular longitudinal cleft in the photograph is an artefact. The photograph was taken after the fetus had been bisected and the two halves laid together again.

FIG. 9. Case 2. Lateral roentgenogram of base of skull and upper vertebrae, showing lordosis of the divided vertebral column. There is a very large foramen magnum.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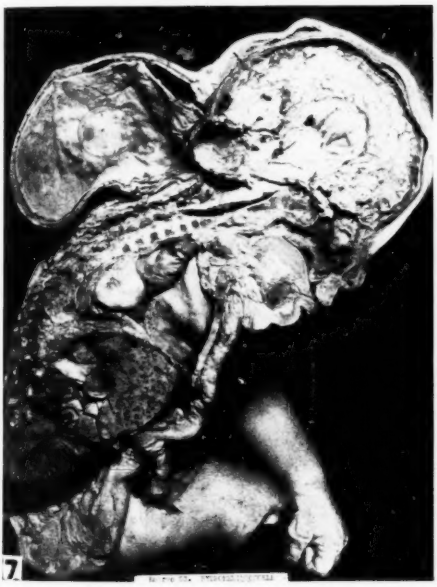
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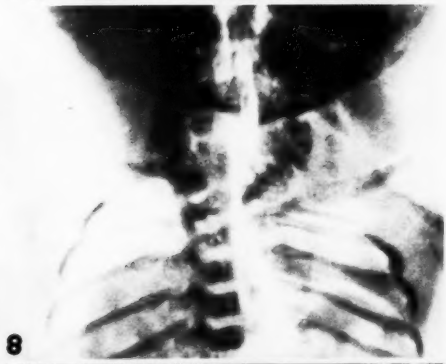
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FOREIGN BODY GIANT CELL GRANULOMA OF THE SPINAL CORD ASSOCIATED WITH SPINA BIFIDA*

BEN W. LICHTENSTEIN, M.D., and JACK D. KIRSHBAUM, M.D.
(From the Department of Neurology and Neurological Surgery, University of Illinois, and the Department of Pathology, Cook County Hospital, Chicago, Ill.)

The case reported in this paper affords a natural reproduction of an experiment previously reported by Hassin.[1] The introduction of a foreign body into any portion of the central nervous system is necessarily associated with the rupture of capillary blood vessels, and the resultant reactive phenomena are, therefore, modified by the admixture of hematogenous elements. In the present case the cellular reaction about fragments of hair located within the substance of the spinal cord was of special interest for the foreign material had entered the nervous system accidentally through an arhaphic defect in the spinal cord and its meninges. There was, in a newborn infant, an ulcerated lumbosacral spina bifida, with exposure of the spinal cord and drainage of spinal fluid. The skin below the cutaneous defect showed hypertrichosis and some fragments of hair had entered the spinal cord, producing a characteristic cellular reaction.

REPORT OF CASE

History. A white female, 33 days of age, born 2 weeks prematurely on May 20, 1939, was admitted to the Cook County Hospital because of the drainage of spinal fluid from a spina bifida in the lumbosacral region.

Examination. The infant was poorly nourished. The essential finding was a mass, 2.5 by 2.5 by 4 cm. in diameter, in the lower lumbar region, surrounded by edematous tissue with spinal fluid escaping through a central defect. The mass bulged when the infant cried and the edges were necrotic.

Course. Ventricular puncture yielded an opalescent fluid under increased pressure. The Pandy reaction was 4 plus and there were 110 cells per cmm. There were 10 mg. of sugar and 600 mg. of chlorides per 100 cc. The culture of the spinal fluid revealed *Staphylococcus aureus*. The child did poorly, developed meningitis and died on July 14, 1939.

Necropsy

The anatomical diagnosis was spina bifida lumbosacralis; marked internal hydrocephalus; cloudy swelling of the kidneys, myocardium and liver; septic softening of the spleen.

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Received for publication December 3, 1940.

There was separation of the cranial bones with enlargement of the skull. Below the cutaneous defect in the lumbosacral region, there was a moderate growth of hair. The cerebral ventricles were dilated, the ependyma was smooth and the cerebral cortex greatly reduced in thickness.

Microscopic Examination

Above the cutaneous defect the spinal cord presented the arhaphic variety of dysrhaphic malformation as described previously by Lichtenstein.[2] It consisted of a flat plate of spinal cord substance lined on its ventral aspect by a greatly thickened and fibrotic pia mater and having in its midportion a rudimentary anterior median fissure containing many blood vessels. Laterally this medullary plate gave rise to large bundles of nerve roots which deviated laterally and ventrally, many of them entering spinal ganglia. The dorsal portion of this medullary plate was composed of gray spinal cord substance rich in capillary blood vessels, the latter merging gradually into a densely fibrotic connective tissue layer which extended into the subcutis. The ventral white columns appeared normal except laterally where there was a moderate increase in fibrillar reticulum. At a more rostral level (Fig. 1) the arhaphic defect was no longer present, the spinal cord being closed dorsally and completely enveloped by leptomeninges.

Under low magnification the dorsal columns were seen to be the site of a spherical mass which completely replaced the spinal cord parenchyma in this region. This mass was encapsulated, sharply separated from the surrounding tissue, and its central portion as well as its capsule were rich in giant cells harboring spherical masses of amorphous material. In some microscopic fields this amorphous material seen in longitudinal section was easily recognized as fragments of hair (Fig. 2). The large cells were of the foreign body giant cell variety consisting of irregular protoplasmic masses containing a variable number of small, round, chromatin-rich nuclei and in some cells as many as twenty-five nuclei were present (Fig. 3). The surfaces of the segments of hair were plastered with innumerable giant cells and in transverse section the hairs appeared to be completely enclosed by them. Where the segments of hair were fine, two por-

tions might be enveloped by a single giant cell, whereas many of the wider strands of hair were only partially enveloped. The central portion of the nodule contained large numbers of distended, fat-laden histiocytes enclosed in a meshwork of reticulum fibrils. The peripheral portions consisted of a dense connective tissue capsule rich in collagen fibers staining deep red by van Gieson's method. Scattered throughout were many giant cells surrounding segments of hair and many naked particles of hair embedded in a dense layer of connective tissue. This nodule was separated from the surrounding spinal cord substance by a narrow zone of fibrillar glia. The spinal cord presented no other changes of significance.

Discussion

From the microscopic findings it is evident that we are dealing with a foreign body giant cell granuloma of the spinal cord, the foreign elements being fragments of hair which had entered the substance of the spinal cord through a defect in the overlying meninges, vertebral neural arch and cutaneous structures. Such defects may be arhaphic in nature, that is, they may result from nonclosure of the primitive neural groove; or they may be dysrhaphic, resulting from defective closure. The fusion defects in such conditions are not restricted to the neural structures but involve the meninges, vertebrae and overlying skin as well. In the case described the spinal cord at one point had developed from the unclosed neural groove. It belongs, therefore, to the arhaphic variety of myelodysplasia. In some instances, as it was in our case, the skin about the cutaneous defect showed hypertrichosis. Some fragments of hair-shafts had entered the spinal cord through the defect in its overlying structures and had penetrated into segments of the cord beyond the site of the arhaphic defect, provoking a characteristic reaction.

The histopathologic changes produced in the spinal cord by the presence of hair were similar to those produced experimentally by the insertion of pledgets of cotton into the cerebral parenchyma of dogs by Oldberg and studied microscopically by Hassin.[1] In these experiments the types of cells present were dependent upon the duration of the experiment. Early, that is, in animals that died from 1 to 8 days after the operation, the reacting cells were

chiefly lymphocytes, plasma cells, macrophages and fibroblasts and no giant cells or gitter cells were seen. In a dog that died after 12 days, fibroblasts and foreign body giant cells were numerous whereas lymphocytes and plasma cells were rare. The microscopic findings in our case were similar to those in the latter experiment. As in Hassin's case, the foreign bodies were plastered by large protoplasmic giant cells or surrounded by fibroblasts. It was readily apparent that the foreign body giant cells could not ingest the particles of hair because of their large size and chemical nature. With the development of fibrocytes and the formation of dense masses of collagenous connective tissue, many of the giant cells had disappeared, leaving the naked hair enveloped in a connective tissue scar. The maturity of the connective tissue response was such as to establish a strong presumption that inclusion of these hairs had occurred before birth and that the resulting granuloma was actually congenital.

Foreign body giant cells developing in the central nervous system are no different from those forming elsewhere in the body. They are undoubtedly mesenchymal in origin and in no way related to the macroglia. When the nervous parenchyma is invaded by smaller foreign elements, as for example the larvae of *Trichinella spiralis*, the reacting cells, according to Hassin and Diamond,[3] are rich in cytoplasm and exclusively glial in nature. According to these authors the majority of these cytoplasmic glial cells fuse, forming syncytia, but in many places glial nodules develop which enclose the trichina larvae. The changes seen in our case were similar to those found when suture material is introduced into the central nervous system.

Localized areas of hypertrichosis over the spine are strongly suggestive of an underlying spina bifida occulta. Pilonidal cysts, dermoid cysts and teratoid tumors are also frequently found. It is important to note, however, that in our case the segments of hair had entered the spinal cord directly and that no evidence of a dermoid tumor was found.

Summary

The microscopic changes produced by the entrance of hair into the substance of the spinal cord are described and the pathogenesis of the lesion resulting from spina bifida is discussed. The ma-

turity of the resulting granuloma in a child, aged 33 days, was such as to indicate that the process was congenital.

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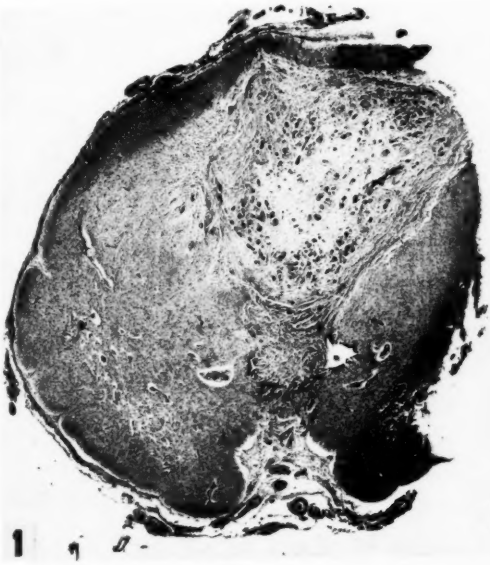
DESCRIPTION OF PLATE

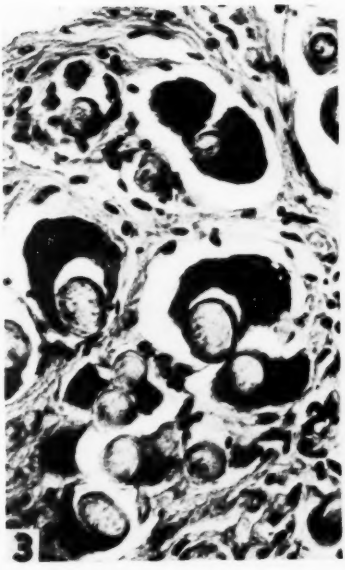
PLATE 140

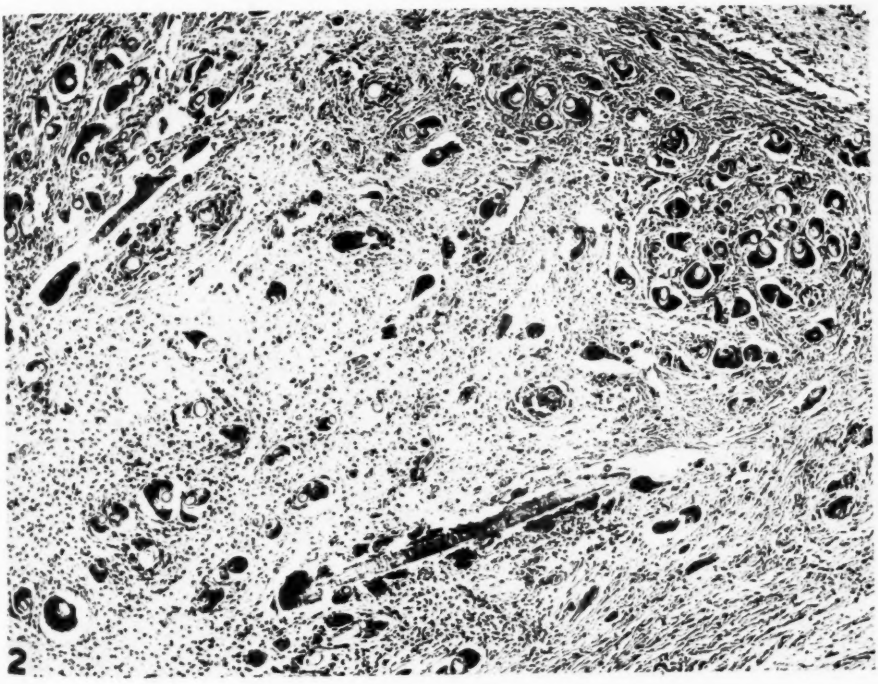
FIG. 1. Low power photomicrograph through the spinal cord at a lumbar level showing the granuloma in its dorsal position. Hemalum and eosin stain. × 40.

FIG. 2. Higher power photomicrograph through a portion of the granuloma seen in Figure 1 showing two hairs in longitudinal section and many others in transverse section surrounded by giant cells. Hemalum and eosin stain. × 300.

FIG. 3. High power photomicrograph showing multinucleated giant cells plastered about segments of hair seen in cross section. Hemalum and eosin stain. × 700.







Lichtenstein and Kirshbaum

Granuloma of Spinal Cord

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EMBOLI OF BRAIN TISSUE IN FETAL LUNGS*

PETER GRUENWALD, M.D.
(From the Department of Anatomy, Chicago Medical School, Chicago, Ill.)

There are but two reports in the literature of fetal pathology of embolism and growth of nervous tissue in the lungs. For this reason, another case of this condition will be described and discussed in this paper.

REPORT OF CASE

Necropsy was done upon the body of a white female infant, 2 days old, measuring 55 cm. and weighing 2600 gm. by Dr. Mary Zeldes at the Department of Pathology of the Cook County Hospital (No. 277–1939). The anatomical diagnosis was: Anencephaly with meningoceles herniating through defects in the frontal bone; congenital cysts of all pulmonary lobes; fatty degeneration and passive congestion of the liver, and passive congestion of the spleen and intestine.

Only the findings related to the subject of this report will be described in detail. The skull was very small. The suture lines were irregular. In the area immediately above the bridge of the nose there was herniation of a soft, cystic, red-purplish mass measuring 30 by 28 by 15 mm. Adjoining this and projecting over the inner canthus of the left eye was another mass measuring 14 by 11 by 7 mm. and of similar consistency and color. The lungs were subcrepitant. Their surfaces were studded with light pink-tan, elevated areas up to 6 mm. in diameter, which collapsed when punctured. On section, the lungs appeared purple-red, with lighter areas similar to the ones on the surface. They were slightly moist with a frothy, bloody fluid. Both pleural cavities were free. The diaphragm was at the third interspace on the left, and at the third rib on the right side.

The necropsy unfortunately was performed under circumstances which gave no opportunity to preserve external parts for later investigation. While the examination of the head was in progress, I was impressed by the peculiar configuration of the skull. It was not that of typical anencephaly; on the contrary, the cranial cavity was, with the exception of the small openings in the frontal bone, closed by bone which was heavier even than

* Received for publication February 28, 1941.

normal. The calvarium was several millimeters thick and no fontanelles were present. The skull was covered by scalp with normal hair. In the cranial cavity, an essentially normal brain stem was found, but there were no definite hemispheres. The meninges continued through the defects in the frontal bone into the two protrusions seen externally on the forehead.

Microscopic examination of the lungs (Figs. 1 and 2) revealed that the foci, referred to as cysts in the gross diagnosis, consisted of an extremely loose tissue in which connective tissue fibrils could not be demonstrated even with an azan stain or silver impregnation. Only from the borders and from structures running through the foci did fibers penetrate into them for a short distance. Cells were scarce in these areas except in the vicinity of other tissues bounding or traversing them. Staining with phosphotungstic acid-hematoxylin revealed fibers not demonstrable with connective tissue stains; they could, therefore, be regarded as glial fibers. This, together with the general structure of the tissue, was evidence that the foci consisted of central nervous tissue, mainly glia. They were sharply separated from the surrounding normal lung tissue and from the pleura by a layer of connective tissue similar to that separating lobules of the lung from each other and from the pleura. Groups of small cavities like compressed alveoli could be seen in a few places at the border of the foci. Ducts lined with high columnar epithelium, and very wide, thin-walled blood vessels, penetrated the foci and divided there into smaller branches (Fig. 2). They were surrounded by scanty connective tissue; no muscle, cartilage, or glands were found in their walls or elsewhere within the foci. No indications of inflammation were seen either in these areas or in the lung tissue surrounding them. The lungs were only partly inflated, in accordance with the short duration of extra-uterine life.

Discussion

The two reports in the literature in which similar disseminated foci of nervous tissue in the lungs are described also record severe malformations of the brain. This is true, also, of two cases* recently observed by Dr. Edith L. Potter at the Chicago Lying-in Hospital. Askanazy [1] was the first to describe this condition in

*To be published. I am indebted to Edith L. Potter for her kindness in showing me sections of the lungs of her cases.

1908. His case differs from the one reported here in the greater growth-intensity of the dislocated nervous tissue, invading lymph vessels of the lung and even a lymph gland. Askanazy considered his case to be one of multiple primary tumors which were not typically malignant. In Hückel's [2] case, a child with a frontal meningocele and comparatively little involvement of the brain lived 4 years. In its lungs, several foci much like those of the present case were found. The nervous tissue had grown into pulmonary alveoli without affecting their walls or any part of the lung. Hückel, therefore, did not regard the foci as tumors. It is possible that in his case the respiratory movements favored the extension of the dystopic tissue into the alveoli.

In the present case, there is not the slightest evidence of tumor-like behavior of the nervous tissue. Its extreme scarcity of cells also indicates a slow rate of growth in the stage observed. It cannot be denied, however, that the tissue, removed from its normal site and not being part of a harmoniously developing organ, may, soon after its deposition in the lungs, have multiplied to a greater extent than under normal circumstances.

The constant coincidence of foci of brain tissue in the lungs with severe changes in the brain points to a close connection between the two as has been assumed by previous observers. A detailed account of the changes in the head may, therefore, be essential for an explanation of the findings in the lungs. In the case here reported, the configuration of the head, including the openings in the frontal bone with meninges herniated through them, gave the impression of being a sequel of a severe injury rather than a malformation caused by intrinsic factors. The latter alternative can be ruled out because no deviation in a developmental process could possibly cause such bilateral openings in the skull and meninges as were found here.

In many human embryos of the late first or second month, as seen following abortions, the brain, which still consists of thin-walled cavities, is ruptured after it had been normally closed and the primordia of meninges and skull formed. In some the neural tube is torn along the line of closure in its dorsal wall. Also openings with protrusion of brain substance can be found in various, irregularly located points. Although it is safe to assume that almost all of these findings in embryos are postmortem artefacts,

they still show that in this period the comparatively thin wall of the ventricles, consisting of the brain and of the primordia of meninges, skull and skin, is, mechanically, a *punctum minoris resistentiae*. The immediate impression upon examining the head of the infant described here, was that it had suffered and survived a rupture of this sort. The findings in the lungs are best explained by the assumption of a blunt injury to the brain, followed by embolism of nervous tissue in the lungs.

Two possibilities of transportation of crushed brain substance to the lungs are to be considered: embolism and aspiration. We can be practically certain that the former happened in this case. Aspiration would require not only respiratory movements, but also a highly developed lung parenchyma. Without alveoli that can expand to many times their collapsed condition, even respiratory movements such as may occur during temporary anoxemia of the embryo could never succeed in bringing particles to the periphery of the lungs immediately underneath the pleura. The findings in the present case give evidence of the incomplete development of the lung parenchyma at the time of the embolism: There was conspicuous growth of the foci with but slight compression of lung tissue, and bronchi grew and branched after the brain tissue had reached the lungs. The shape of the foci and of the bronchi in them and the absence of compressed lung parenchyma around the bronchi are in favor of growth of the bronchi into the brain tissue rather than enlargement of the foci around bronchi already surrounded by alveoli. The vascular network of the lungs, on the other hand, must have been quite well developed at the time of the embolism. Only this can explain the presence of so many scattered and well isolated foci. We may, therefore, limit the time at which the anomaly in question originated to a period after the establishment of a complex system of capillaries in the lungs and before the formation of the definitive lung tissue. This coincides with the previously mentioned period of great vulnerability of the brain. Consequently, we may conclude that, during the second month of pregnancy, trauma caused the skull to rupture in the frontal region, destroyed part of the brain and at the same time forced particles of brain into the circulation. In later stages the brain and its coverings are comparatively much stronger and an injury leading to their rupture could scarcely be survived.

As was mentioned before, the relations of the nervous tissue to the bronchi and the surrounding lung parenchyma make it highly probable that the bronchi grew into the brain tissue. They branched in the abnormal surroundings, but did not form alveoli or other respiratory surfaces. Likewise no cartilage, muscle or glands were developed in their walls. This may be an indication that normally an influence of, or an interaction with, normal amounts of mesenchyme has to occur in order to enable full development of bronchial walls and formation of respiratory structures. The brain tissue grew, according to the pictures seen, in a benign manner and was indifferent to the surrounding lung tissue.

Both Askanazy and Hückel favored the assumption of embolism against aspiration, for reasons similar to those given. In all cases, including those observed by Potter, dystopic nervous tissue was found in the lungs exclusively. Fetal circulation, however, unlike that of the adult, must have deposited brain particles in other organs too, owing to the communication between pulmonary artery and aorta established by the ductus arteriosus. It seems that conditions in the lungs are more favorable for growth of such emboli than in any other organ. It cannot be determined what property of the embryonic lung tissue accounts for this peculiarity.

The findings in the skull of this case illustrate the moulding influence of the brain upon its bony capsule. The skull, primarily formed to cover a normal brain, was not exposed to the pressure of growing hemispheres after the injury. As a consequence, the bones reached each other earlier, leaving no fontanelles between them. It cannot be decided whether their abnormal thickness is due to the distribution of the normal amount of bone over an abnormally small surface, or to a diminution of normal bone resorption because of reduced intracranial pressure.

Summary

Multiple foci of brain tissue were found in the lungs of a newborn infant with frontal meningoceles and a severe defect of the brain. As is evident from four reports of very similar cases gathered from the literature and personal communications, such foci in the lungs occur only in association with rather severe disturbances in the structure of brain and skull.

It is considered most probable that during the second month

of embryonic life a blunt injury caused the brain to rupture and that this was followed by embolism of multiple particles of nervous tissue in the lungs. No evidence of tumor-like growth of the foci in the lungs could be obtained.

NOTE: I wish to acknowledge the kindness of Walter Schiller, Director of Laboratories of the Cook County Hospital, in permitting me to describe this case.

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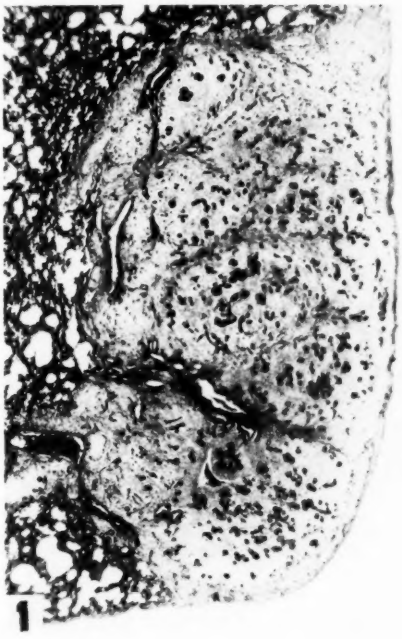
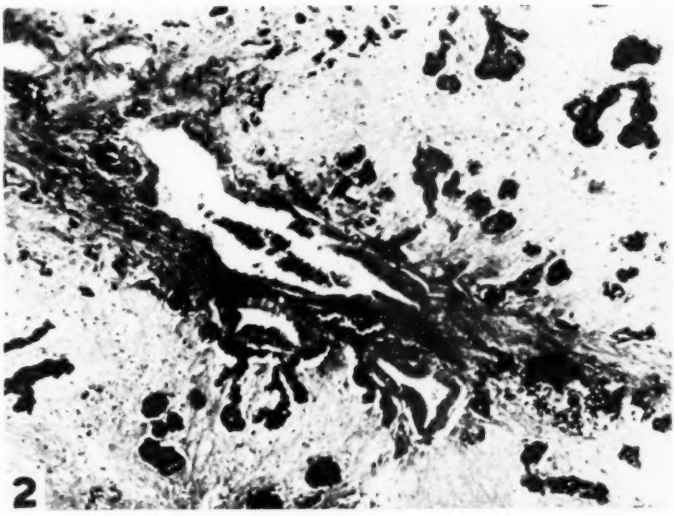
DESCRIPTION OF PLATE

PLATE 141

FIG. 1. Photomicrograph of one of the foci of nervous tissue in the lungs. Azan stain. × 18.

FIG. 2. Part of the same section shown in Figure 1, showing bronchi lined with high columnar epithelium, and congested thin-walled blood vessels in a loose glial stroma with few cells. × 100.





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UNIV. OF PITT.

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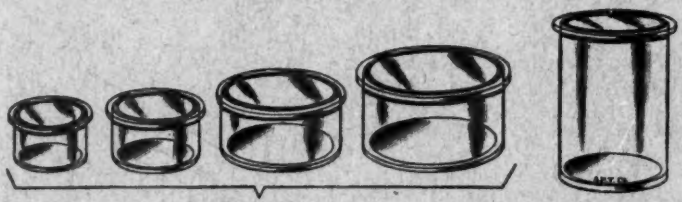

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